The attached Medwatch reports do not contain any potential follow- up to initial reports received through telephone report.

MedWatch Forms

(USA)

Patient Number 1

3651386-7-00-01

Aventis Pharma, Inc.

Approved by FDA on 3/22/94

MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Mfr report # 20011008 5US

Page 1 of 3

FDA Use Only

A. Patient information

1. Patient identifier: AE
2. Age at time of event: 29 yrs (or Date of birth: 04/13/1971)
3. Sex: female / male
4. Weight: _____ lbs or _____ kgs

in confidence

B. Adverse event or product problem

1. Adverse event and/or Product problem (e.g., defects/malfunctions)
2. Outcomes attributed to adverse event (check all that apply)
   - death 01/03/2001
   - life-threatening
   - hospitalization - initial or prolonged
   - disability
   - congenital anomaly
   - required intervention to prevent permanent impairment/damage
   - other:
3. Date of event: 12/??/2000
4. Date of this report: 01/17/2001
5. Describe event or problem

	Event (Nature of Event)	Dx Origin
(Dx)	FULMINANT HEPATIC FAILURE (FATAL)	Reporter
(Sx)	INCREASED SGOT >2000	
(Sx)	INCREASED SGPT >2000	
(Sx)	INCREASED ALKALINE PHOSPHATASE 153	
(Sx)	INCREASED BILIRUBIN 31	
(Dx)	DISSEMINATED INTRAVASULAR COAGULATION (FATAL)	Reporter
(Dx)	PERI-RECTAL HERPETIC ERUPTIONS SUGGESTING HERPETIC HEPATITIS	Reporter

Narrative: Initial report: This postmarketing case from the US was received from a physician and involves a 29-year-old female patient who initiated therapy with *

6. Relevant tests/laboratory data, including dates

7. Other relevant history, including preexisting medical conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)

ADULT ONSET STILL'S DISEASE, IMMUNOSUPPRESSED, MARIJUANA USE, POSSIBLE ALCOHOL ABUSE, alcohol use, drug abuse history
PCP PROPHYLAXIS
JOINT PAINS

C. Suspect medication(s)

1. Name (give labeled strength & mfr/labeler if known)
   - #1 LEFLUNOMIDE (ARAVA) Tablets
   - #2
2. Dose, frequency & route used
   - #1 20 MG/DAY PO
   - #2
3. Therapy dates (if unknown, give duration)
   - #1 Duration: 3 months
   - #2
4. Diagnosis for use (indication)
   - #1 ADULT ONSET STILL'S DISEASE
   - #2
5. Event abated after use stopped or dose reduced
   - #1 yes / no / doesn't apply
   - #2 yes / no / doesn't apply
6. Lot # (if known)
   - #1
   - #2
7. Exp. date (if known)
   - #1
   - #2
8. Event reappeared after reintroduction
   - #1 yes / no / doesn't apply
   - #2 yes / no / doesn't apply
9. NDC # - for product problems only (if known)
   - #1
   - #2
10. Concomitant medical products and therapy dates (exclude treatment of event)

ATOVAQUONE
AZITHROMYCIN
CALCIUN
METHYLPREDNISOLONE (MEDROL) *

G. All manufacturers

1. Contact office - name/address (& mfr/lng site for devices)

Aventis Pharma, Inc.
10236 Marion Park Drive
Kansas City, MO
64137

2. Phone number: (816) 966-5000

3. Report source (check all that apply)
   - foreign
   - study
   - literature
   - consumer
   - X health professional
   - user facility
   - company representative
   - distributor
   - other:

4. Date received by manufacturer: 01/08/2001

5. (A)NDA # 20-905
   IND #
   PLA #
   pre-1938 yes
   OTC product yes

6. If IND, protocol #

7. Type of report (check all that apply)
   - 5-day X 15-day
   - 10-day periodic
   - Initial X follow-up # 1

8. Adverse event term(s)

HEPATIC FAILURE, ASPARTATE AMINOTRANSFERASE INCREASED, ALANINE AMINOTRANSFERASE INCREASED, BLOOD ALKALINE PHOSPHATASE NOS INCREASED, *

9. Mfr report number: 20011008 5US

E. Initial reporter

1. Name, address & phone #

ROBERT SANDS Dr
111 GROSSMAN DR
BRAINTREE, MA 02184
UNITED STATES 481-849-2265

2. Health professional? yes / no
3. Occupation
4. Initial reporter also sent report to FDA: yes / no / unk

DSS
JAN 2 2 2001

FDA

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

Item completed on continuation pages

JAN 1 9 2001

B.5. Describe event or problem

(continuation:) Arava (leflunomide) 20 mg daily (unknown if loading dose was given) approximately 2-3 months ago for adult onset Still's disease. Significant medical history includes very difficult adult onset Still's disease treated with many immunosuppressive medications, immunosuppressed, marijuana use and possible alcohol abuse. Concomitant medications include atovaquone, azithromycin, calcium, methylprednisolone, multivitamins, oxycodone/acetaminophen and infliximab. The patient's liver enzymes were markedly elevated in early Dec 2000. At some point it was discovered that her dose of atovaquone (patient was not HIV positive) was three times the prescribed dose due to a medication error. Cholestyramine was initiated on 10 Dec, but the patient only took 4g three times a day and did not complete the course. She did not return for repeat lab tests on 21 Dec. Jaundice was noted on 24 Dec but the patient refused hospital admission. The patient was admitted to the hospital on 27 Dec and had a rapidly progressive downhill course. On admission SGOT 1574, SGPT 1679, Alk Phos 153, Amylase 103, Bilirubin 31, Lipase 426 and Albumin 2.4. Cholestyramine was re-started. The patient developed disseminated intravascular coagulapathy and clotted off the supply to the liver. PTT 123 (22-34), PT 32 (11-13), INR went from 1.03 to 5 (dates unknown). Toxicology screen was positive only for opiates (she had received oxycodone/acetaminophen for joint pain). Blood cultures were negative; urine and sputum were positive for yeast. Peri-rectal herpetic eruptions were noted which suggested the possibility of herpetic hepatitis. Liver biopsy was not performed as it was considered too dangerous. Hepatitis A, B and C were negative. At the end of Dec (date unknown) SGOT and SGPT were in the "2000 range", Creatinine 2.1, CO2 8.0 and Albumin was 1.0. She was transferred to the clinic for evaluation for a liver transplant but died on 3-Jan-2001 of fulminant hepatic failure. The reporter will request an autopsy. The reporter indicated that the hepatic toxicity could have been related to Arava, liver compromise due to alcohol use and other medications, immunosuppression, herpetic hepatitis, the patient's underlying Still's disease or a combination of all factors. Further information is requested.

Addendum for 08-Jan-01: Follow-up information received from Lab Corp.via a physician. Demographics were provided. Physician reported that the patient was transferred to Lahey Clinic for transplant. The reporting physician saw the patient for 2 days prior to transfer and recalled that the patient was treated with "pressors to maintain blood pressure" (nos). Work-up for infection was negative. Three liver ultrasounds were done, however, reporter did not have results. No further information was provided.

Addendum for 16-Jan-01: Follow-up information was received from a sales representative. The patient was number 1 on the list in New England for a liver transplant, but died before the transplant could be performed. Autopsy was not performed. The physician indicated that after "reviewing all the data, he does not believe the hepatic failure was due to Arava", however, he gave no other specific alternative explanation.

Event	Serious	Dechal	Rechal	Rpt.Causality	Alternative Explanation
(Dx) FULMINANT HEPATIC FAILURE (FATAL)	YES	NO	NA	Unlikely	possibly associated with concomitant drug(s)
(Sx) INCREASED SGOT >2000					
(Sx) INCREASED SGPT >2000					
(Sx) INCREASED ALKALINE PHOSPHATASE 153					
(Sx) INCREASED BILIRUBIN 31					
(Dx) DISSEMINATED INTRAVASCULAR COAGULATION (FATAL)	YES	NO	NA		possibly associated with concomitant drug(s)
(Dx) PERI-RECTAL HERPETIC ERUPTIONS SUGGESTING HERPETIC HEPATITIS	NO	NO	NA		underlying/concomitant illness

DSS

JAN 2 2 200

JAN 1 9 2001

B.5. Describe event or problem

[continuation:]

C.10. Concomitant medical products and therapy dates (exclude treatment of event)

[continuation:] ERGOCALCIFEROL, ASCORBIC ACID, FOLIC ACID, THIAMINE HYDROCHLORIDE, RETINOL, RIBOFLAVIN, NICOTINAMIDE, PANTHENOL (MULTIVITAMINS)
PARACETAMOL, OXYCODONE HYDROCHLORIDE, OXYCODONE TEREPHTHALATE (PERCOCET)
INFLIXIMAB (REMICADE)

G.8. Adverse event term(s)

[continuation:] BLOOD BILIRUBIN INCREASED, DISSEMINATED INTRAVASCULAR COAGULATION, HERPES VIRAL INFECTION NOS

MedWatch Forms

(USA)

Patient Number 2

Individual Safety Report

3645714-6-00-01

Aventis Pharma, Inc.

Domain Facsimile — Approved by FDA on 3/22/94

Mfr report # 20002091 4US

LF/Dist report #

FDA Use Only

MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

A. Patient information

1. Patient Identifier	2. Age at time of event	3. Sex	4. Weight
TGB	51 yrs	☒ female	____ lbs
in confidence	or ____	☐ male	or
	Date of birth: UNK		____ kgs

B. Adverse event or product problem

1. ☒ Adverse event and/or ☐ Product problem (e.g., defects/malfunctions)

2. Outcomes attributed to adverse event (check all that apply)

- ☒ death 11/10/2000 (mo/day/yr)
- ☐ life-threatening
- ☒ hospitalization - initial or prolonged
- ☐ disability
- ☐ congenital anomaly
- ☐ required intervention to prevent permanent impairment/damage
- ☒ other: *

3. Date of event (mo/day/yr): 09/05/2000

4. Date of this report (mo/day/yr): 01/08/2001

5. Describe event or problem

Event (Nature of Event)	Dx Origin
(Dx) ACUTE HEPATIC NECROSIS	Reporter
(Sx) INCREASED ALT 600	
(Sx) INCREASED AST 400	
(Sx) INCREASED BILIRUBIN 17	
(Sx) INCREASED ALKALINE PHOSPHATASE >1400	
(Sx) JAUNDICE	
(Sx) FEVER NOS	
(Sx) MACULOPAPULAR RASH	Reporter
(Dx) ATELECTASIS	Reporter
(Sx) FEVER NOS	
(Sx) PLEURITIC PAIN	
(Dx) INCREASED COAGULOPATHY	Reporter
(Sx) INCREASED PROTIME 27	
(Dx) RED CELL APLASIA	Reporter
(Dx) FEVER (104)	Reporter *

6. Relevant tests/laboratory data, including dates

7. Other relevant history, including preexisting medical conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)

NO MENTION OF RELEVANT DISEASE
unk

C. Suspect medication(s)

1. Name (give labeled strength & mfr/labeler, if known)

#1 LEFLUNOMIDE (ARAVA) Tablets

#2 LEFLUNOMIDE (ARAVA) Tablets

2. Dose, frequency & route used	3. Therapy dates (if unknown, give duration) from/to (or best estimate)
#1 100 MG QD PO	#1 *
#2 20 MG/DAY PO	#2 08/07/2000 to ??/??/2000

4. Diagnosis for use (indication)

#1 RHEUMATOID ARTHRITIS

#2 RHEUMATOID ARTHRITIS

5. Event abated after use stopped or dose reduced

#1 ☐ yes ☐ no ☒ doesn't apply

#2 ☐ yes ☐ no ☒ doesn't apply

6. Lot # (if known)	7. Exp. date (if known)
#1	#1
#2	#2

8. Event reappeared after reintroduction

#1 ☐ yes ☐ no ☒ doesn't apply

#2 ☐ yes ☐ no ☒ doesn't apply

9. NDC # - for product problems only (if known)

#1 #2

10. Concomitant medical products and therapy dates (exclude treatment of event)

CELECOXIB ??/??/2000 to Unknown
PREDNISONE

G. All manufacturers

1. Contact office - name/address (& mfr/mg site for devices)

Aventis Pharma, Inc.
10236 Marion Park Drive
Kansas City, MO
64137

2. Phone number: (816) 966-5000

3. Report source (check all that apply)

- ☐ foreign
- ☐ study
- ☐ literature
- ☐ consumer
- ☒ health professional
- ☐ user facility
- ☐ company representative
- ☐ distributor
- ☐ other

4. Date received by manufacturer (mo/day/yr): 12/29/2000

5. (A)NDA # 20-905
IND # ____
PLA # ____
pre-1938 ☐ yes
OTC product ☐ yes

6. If IND, protocol #

7. Type of report (check all that apply)

- ☐ 5-day ☒ 15-day
- ☐ 10-day ☐ periodic
- ☐ initial ☒ follow-up # 7

8. Adverse event term(s)

HEPATIC NECROSIS, ALANINE AMINOTRANSFERASE INCREASED, ASPARTATE AMINOTRANSFERASE INCREASED, BLOOD BILIRUBIN INCREASED, BLOOD ALKALINE *

9. Mfr. report number: 200020914US

E. Initial reporter

1. Name, address & phone #

GRISANTI MD
UNITED STATES

2. Health professional? ☒ yes ☐ no

3. Occupation

4. Initial reporter also sent report to FDA ☐ yes ☐ no ☐ unk

FDA

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

* Item completed on continuation pages.

JAN 16 2001

Individual Safety Report

3645714-6-00-02

Aventis Pharma, Inc.

Domain Facsimile — Approved by FDA on 3/22/94

Mfr report # 20002091408

UF/Dist report #

FDA Use Only

MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

A. Patient information

1. Patient identifier	2. Age at time of event: / Date of birth:	3. Sex	4. Weight
TGB in confidence	or	☐ female ☐ male	____ lbs or ____ kgs

B. Adverse event or product problem

1. ☐ Adverse event and/or ☐ Product problem (e.g., defects/malfunctions)

2. Outcomes attributed to adverse event (check all that apply)
- ☐ death ____ (mo/day/yr)
- ☐ life-threatening
- ☐ hospitalization - initial or prolonged
- ☐ disability
- ☐ congenital anomaly
- ☐ required intervention to prevent permanent impairment/damage
- ☐ other: ____

3. Date of event (mo/day/yr)

4. Date of this report (mo/day/yr)

5. Describe event or problem

6. Relevant tests/laboratory data, including dates

7. Other relevant history, including preexisting medical conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)

C. Suspect medication(s)

1. Name (give labeled strength & mfr/labeler, if known)
- #3 CELECOXIB (CELEBREX)
- #4

2. Dose, frequency & route used
- #3 200 MG/DAY
- #4

3. Therapy dates (if unknown, give duration) (mo/da/yr for best estimate)
- #3 ??/??/2000 to Unknown
- #4

4. Diagnosis for use (indication)
- #3 RHEUMATOID ARTHRITIS
- #4

5. Event abated after use stopped or dose reduced
- #3 ☐ yes ☐ no ☐ doesn't apply
- #4 ☐ yes ☐ no ☐ doesn't apply

6. Lot # (if known)
- #3
- #4

7. Exp. date (if known)
- #3
- #4

8. Event reappeared after reintroduction
- #3 ☐ yes ☐ no ☐ doesn't apply
- #4 ☐ yes ☐ no ☐ doesn't apply

9. NDC # - for product problems only (if known)
- #3
- #4

10. Concomitant medical products and therapy dates (exclude treatment of event)

G. All manufacturers

1. Contact office - name/address (& mfrng site for devices)

2. Phone number

3. Report source (check all that apply)
- ☐ foreign
- ☐ study
- ☐ literature
- ☐ consumer
- ☐ health professional
- ☐ user facility
- ☐ company representative
- ☐ distributor
- ☐ other:

4. Date received by manufacturer (mo/day/yr)

5. (A)NDA # ____
IND # ____
PLA # ____
pre-1938 ☐ yes
OTC product ☐ yes

6. If IND, protocol #

7. Type of report (check all that apply)
- ☐ 5-day ☐ 15-day
- ☐ 10-day ☐ periodic
- ☐ Initial ☐ follow-up #____

8. Adverse event term(s)

9. Mfr. report number

E. Initial reporter

1. Name, address & phone #

2. Health professional?
- ☐ yes ☐ no

3. Occupation

4. Initial reporter also sent report to FDA
- ☐ yes ☐ no ☐ unk

FDA

Domain Facsimile of FDA Form 3500A

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

* Item completed on continuation pages.

JAN 1 0 2001

B.2. Other outcome

medically important

B.5. Describe event or problem

[continuation:] (Dx) SEVERAL FEBRILE EPISODES Reporter
(Dx) DUODENAL ULCER Reporter
(Sx) GASTROINTESTINAL BLEED
(Sx) POOR NUTRITION
(Sx) ALBUMIN LOW
(Dx) PERFORATED ULCER Reporter
(Dx) LEFT LOWER LOBE PNEUMONIA Reporter
(Dx) PERITONITIS Reporter
(Dx) SEPTIC SHOCK FATAL OUTCOME Reporter
(Dx) DEHISCENCE Reporter

Narrative: Initial report: This postmarketing case from US received from Lab Corp via physician + involves 51 yr old female who received Arava (leflunomide) 20 mg daily for rheumatoid arthritis (insidous synovitis + rheumatoid factor negative) beginning approx. 4-5 months ago. Not known if patient received loading dose of leflunomide. Medical history is not reported. Concomitant medication includes celecoxib. Reporter states approx. 05-Sep-00 pt. was hospitalized due to rash, fever, pleuritic pain, + jaundice. Rash + fever had started approximately 2 weeks prior to hospitalization. Leflunomide + celecoxib were discontinued at that time + she was prescribed cholestyramine 8 grams three times a day. Initially discharged from hospital after first admission but was subsequently readmitted on unknown date due to fever. During second hospitalization she was noted to have atelectasis, abnormal liver function tests and increased protime (27). Diagnosis of acute hepatic necrosis was made. She was transferred to another facility for evaluation for liver transplant. Reporter's assessment of causal relationship is that it cannot be excluded.

Lab Data	Date not provided
ALT	600
AST	400
PROTIME	27.1
PTT	31.4
BILI	9.0
ALK PHOS	270
ALBUMIN	2.2

Add 25-Sep-00: Info. rec'd from reporter: Clinically stabilizing 21-Sept-00. LFTs + prothrombin time decreasing. "The patient doing better". 3 leflunomide plasma levels drawn, last being greater than 1. Reporter unsure MD will continue cholestyramine. As of 21-Aug-00, had not undergone liver transplant + scheduled for liver biopsy on 22-Sept-00. Had multiple CT scans and ultrasounds.

Add 2-Oct-00: MD was contacted + provided: Fever 104 F last weekend + blood count low. Not sure patient was transfused. Liver biopsy scheduled 22-Sept-00 cancelled + reporter unsure biopsy took place. No info. in regards to the pathology of liver.

Add 6-Oct-00: Discharged Cleveland Clinic 29-Sep-00 + to be followed by primary MD. LFT's + CBC to be monitored. Reporter: liver biopsy showed inflammation. Awaiting results of bone marrow biopsy.

Add 11-Oct-00: Info. rec'd from MD. Liver biopsy showed centrilobular necrosis w/ portal inflammation + hepatic necrosis consistent w/ drug reaction. Pt. did not have liver transplant as Cleveland Clinic felt pt. had enough liver tissue left to regenerate. Bone marrow biopsy revealed red cell aplasia + treated w/ plasma products to correct low blood count. Highest transaminases recorded were >1000, alkaline phosphatase >1400 and bilirubin 17 (dates not provided). Bili. decreased to 12 + transaminases improving, still high. Had 10 day course of cholestyramine but leflunomide levels remain elevated. Concomitant drug celecoxib is suspect drug.

B.5. Describe event or problem

[continuation:] ADD 25-OCT-00: F/U rec'd from nurse in MD's office. Pt. had several febrile episodes since discharge from Cleveland Clinic necessitating laboratory work as outpatient. Admitted to hosptiatl for gastrointestianl bleed, week-end of 21-Oct-00. Reporter believes she was transfused, not confirmed by MD. Arava level 11-Oct-00, 2.7. Reporter believes she underwent 2 washout procedures. Had bone marrow + liver cultures (looking for tuberculosis) in Cleveland, awaiting results.

ADD 27-OCT-00: F/U via voice mail from Rheu.Sales Rep. provides albumin levels low (nos)+ nutrition poor, not ingesting anything orally. Has duodenal ulcer.

ADD 31-OCT-00: Reporter rec'd verbal report: results of liver + bone marrow cultures neg. for TB.

ADD 08-NOV-00: Perforated ulcer + GI bleed approx. 26-Oct. Surgery done 27 or 28-Oct-00. Taking + retaining food orally. Developed left lower lobe pneumonia post-op (end Oct or beg. Nov). Pneumonia treated + resolving. Still jaundiced, liver functions improving: bili. = 14. Arava level 31-Oct = 0.7. Improving, out of bed.

ADD 13-NOV-00: Info. provides: Discharged 08-Nov-00 after successful surgery from GI bleed. After discharge, "incision opened and contents of stomach went into abdomen which led to peritonitis". Returned to hospital for emergency surgery. Went into septic shock + died 10-Nov-00.

Add 07-Dec-00: Arava dc'd prior to 07-Sep-00 (first Questran rx). Rec'd for less than 1 month. Celebrex began approx. 2 weeks prior to 14-Jul-00. Rec'd 30 doses Questran over several weeks, level was 6. MD feels stress ulcer from steroid therapy, fever, debilitation, poor nutrition.Several bleeding sites found. Angiogram + attempt to thrombose left gastric artery, unsuccessful. Surgery to tie off bleeders. Arava level was 1. Fever returned w/ tapering steroids. 2 days post discharge, returned in septic shock, dehiscence of pyloroplasty, + peritonitis Succumbed after surgery due to GI bleed and complications. MD assessed dehiscence due to hypoalbuinemia + steroids. 2 biopsies: no evidence of chronic liver disease no fibrosis or cirrhosis. Imp. both biopsies: acute hepatitis w/ some necrosis. First bx Cleveland + MD felt she would recover. Hep A, B, + C neg. No hx alcohol problem. Refractory fever during illness, treated w/ tylenol + steroids. Cultures neg. No autopsy done. MD: assesses hepatic necrosis caused by Arava. Celebrex may have contributed, or poss. combination.

ADD 13-Dec-00: MD assessed Arava as cause of hepatic necrosis. Added: gastro. + CC felt the same. Assessed Celebrex as not related to events.

ADD 29-Dec-00: MD from Cleveland reports he saw pt for 4 days during 11 days in CC. Bone marrow: hypercellular, no evidence of malignancy, some polyclonal plasmacytosis, erythroid hypoplasia. Biopsy: mild portal + lobular hepatitis, centrilobular hepatocyte necrosis.

	19-Sep	28-Sep
AST	334	238
ALT	675	585
ALK PHOS	284	426
BILI	13.1	16

CAUSALITY: possibily related due to temporal relationship.

Case edited due to space.

Event	Serious	Dechal	Rechal	Rpt.Causality	Alternative Explanation	
(Dx) ACUTE HEPATIC NECROSIS	YES	NA	NA	Possible	possibly associated with	*

B.5. Describe event or problem

[continuation:]

					concomitant drug(s)
(Sx) INCREASED ALT 600					
(Sx) INCREASED AST 400					
(Sx) INCREASED BILIRUBIN 17					
(Sx) INCREASED ALKALINE PHOSPHATASE >1400					
(Sx) JAUNDICE					
(Sx) FEVER NOS					
(Dx) MACULOPAPULAR RASH	YES	NA	NA	Possible	possibly associated with concomitant drug(s)
(Dx) ATELECTASIS	YES	NA	NA	Possible	underlying/concomitant illness
(Sx) FEVER NOS					
(Sx) PLEURITIC PAIN					
(Dx) INCREASED COAGULOPATHY	YES	NA	NA	Possible	underlying/concomitant illness
(Sx) INCREASED PROTIME 27					
(Dx) RED CELL APLASIA	YES	NA	NA		
(Dx) FEVER (104)	YES	NA	NA		underlying/concomitant illness
(Dx) SEVERAL FEBRILE EPISODES	NO	NA	NA		underlying/concomitant illness
(Dx) DUODENAL ULCER	YES	NA	NA		possibly associated with concomitant drug(s)
(Sx) GASTROINTESTINAL BLEED					
(Sx) POOR NUTRITION					
(Sx) ALBUMIN LOW					
(Dx) PERFORATED ULCER	YES	NA	NA		possibly associated with concomitant drug(s)
(Dx) LEFT LOWER LOBE PNEUMONIA	YES	NA	NA		other known or suspected cause
(Dx) PERITONITIS	YES	NA	NA		other known or suspected cause
(Dx) SEPTIC SHOCK FATAL OUTCOME	YES	NA	NA		other known or suspected cause
(Dx) DEHISCENCE	YES	NA	NA		other known or suspected cause

C.3. Therapy dates (if unknown, give duration) (mo/day/yr) (Suspect #1)

08/04/2000 to 08/06/2000 Duration: 3 days

G.8. Adverse event term(s)

[continuation:] PHOSPHATASE NOS INCREASED, JAUNDICE NOS, PYREXIA, RASH MACULO-PAPULAR, ATELECTASIS, PYREXIA, PLEURITIC PAIN, COAGULATION DISORDER NOS, PROTHROMBIN TIME PROLONGED, RED CELL APLASIA, PYREXIA, PYREXIA, DUODENAL ULCER, GASTROINTESTINAL HAEMORRHAGE NOS, MALNUTRITION NOS, BLOOD ALBUMIN DECREASED, INTESTINAL ULCER PERFORATION NOS, LOBAR PNEUMONIA NOS, PERITONITIS, SEPSIS NOS, WOUND DEHISCENCE

MedWatch Forms

(USA)

Patient Number 3

Individual Safety Report

3486831-3-00-01

Aventis Pharma, Inc.

Domain Facsimile — Approved by FDA on 3/22/94

Mfr report # 200011168HMRI

UF/Dist report #

FDA use Only

MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Patient information

1. Patient identifier	2. Age at time of event:	3. Sex	4. Weight
BF	53 yrs	☒ female	____ lbs
in confidence	or Date of birth: 07/11/1946	☐ male	or ____ kgs

B. Adverse event or product problem

1. ☒ **Adverse event** and/or ☐ **Product problem** (e.g., defects/malfunctions)

2. **Outcomes attributed to adverse event** (check all that apply)

- ☐ death ____ (mo/day/yr)
- ☒ life-threatening
- ☐ hospitalization - initial or prolonged
- ☐ disability
- ☐ congenital anomaly
- ☐ required intervention to prevent permanent impairment/damage
- ☐ other: ____

3. Date of event (mo/day/yr)	4. Date of this report (mo/day/yr)
05/??/1999	04/06/2000

5. Describe event or problem

Event (Nature of Event)	Dx Origin
(Dx) LOST TASTE BUDS (Overdose)	Reporter
(Dx) ELEVATED LIVER ENZYMES NOS (Overdose)	Reporter
(Dx) BAD BACK ACHE (Overdose)	Reporter
(Dx) COMPLETE LIVER FAILURE (Overdose)	Reporter
(Sx) COMA	
(Dx) WEIGHT LOSS (Overdose)	Reporter
(Dx) TONGUE BURNING (Overdose)	Reporter

Narrative: Initial report: This postmarketing case from the US was received *

6. Relevant tests/laboratory data, including dates

7. Other relevant history, including preexisting medical conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)

SMOKER, nicotine use

APR 12 2000

C. Suspect medication(s)

1. Name (give labeled strength & mfr/labeler, if known)

#1 LEFLUNOMIDE (ARAVA) Tablets

#2 LEFLUNOMIDE (ARAVA) Tablets

2. Dose, frequency & route used	3. Therapy dates (if unknown, give duration) from/to (or best estimate)
#1 100 MG QD PO	#1 *
#2 100 MG QD PO	#2 *

4. Diagnosis for use (indication)	5. Event abated after use stopped or dose reduced
#1 RHEUMATOID ARTHRITIS	#1 ☐ yes ☐ no ☐ doesn't apply
#2 RHEUMATOID ARTHRITIS	#2 ☐ yes ☐ no ☐ doesn't apply

6. Lot # (if known)	7. Exp. date (if known)	8. Event reappeared after reintroduction
#1	#1	#1 ☐ yes ☐ no ☐ doesn't apply
#2	#2	#2 ☐ yes ☐ no ☐ doesn't apply

9. NDC # - for product problems only (if known)

#1 #2

10. Concomitant medical products and therapy dates (exclude treatment of event)

SULFASALAZINE (AZULFIDINE)
MISOPROSTOL (CYTOTEC)
PREDNISONE

G. All manufacturers

1. Contact office - name/address (& mfr'ing site for devices)

Aventis Pharma, Inc.
10236 Marion Park Drive
Kansas City, MO
64137

APR 11 2000

2. Phone number: (816) 966-5000

3. Report source (check all that apply)

- ☐ foreign
- ☐ study
- ☐ literature
- ☐ consumer
- ☐ health professional
- ☐ user facility
- ☐ company representative
- ☐ distributor
- ☐ other

4. Date received by manufacturer (mo/day/yr)	5.
03/30/2000	(A)NDA # 20-905
6. If IND, protocol #	IND # ____
	PLA # ____
7. Type of report (check all that apply)	pre-1938 ☐ yes
☐ 5-day ☐ 15-day	OTC product ☐ yes
☐ 10-day ☐ periodic	
☐ Initial ☐ follow-up # ____	

8. Adverse event term(s)

TONGUE DISORDER, LIVER FUNCTION TEST ABNORMAL, BACK PAIN LIVER FAILURE, COMA, WEIGHT LOSS, TONGUE PAIN

9. Mfr. report number

200011168HMRI

E. Initial reporter

1. Name, address & phone #

BECKY FYFFE MS
216 LAKEVIEW DRIVE SOUTH
MARSHALL, TX 75672
UNITED STATES 903-938-3049

2. Health professional?	3. Occupation	4. Initial reporter also sent report to FDA
☐ yes ☐ no		☐ yes ☐ no ☐ unk

FDA

Domain Facsimile of FDA Form 3500A

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

* Item completed on continuation pages

B.5. Describe event or problem

[continuation:] from a 53 year old consumer who reports that she was receiving Arava (leflunomide) 100mg for rheumatoid arthritis from Apr-99 until May-99 and experienced loss of taste buds. She discontinued the leflunomide and recovered from the event. At a later time in June or July of 1999, she saw her rheumatologist who recommended she resume therapy with Arava, 100mg once a day. She reports taking a total of 87 days at this dose. In approximately June she had liver function tests performed and was told that her liver enzymes were elevated (NOS) and she was instructed to continue to take Arava. On 12-Aug-99 she was seen because of a bad back ache located bilaterally in her kidney areas. On 13-Aug-99 she was hospitalized for "complete liver failure" and went into a coma. She also reports weight loss and tongue burning during this time. She was discharged on 21-Aug-99 and received lactulose until Feb-00. The patient states that in Feb-00 she underwent a liver biopsy which revealed her liver damage had resolved. The patient denies any previous liver problems and refused permission to contact her physician. Further information has been requested, however is not anticipated. Significant medical history includes smoking. Concomitant medications include sulfasalazine, misoprostol and prednisone. This report has not been substantiated by a healthcare professional.

Reporter assessment of the causal relationship between the adverse event and suspect drug:
[_] Possible [_] Unlikely [_] Unrelated
[_] Insufficient Data
If unlikely/unrelated, provide alternative explanation:
[_] Illness [_] Concomitant Drug [_] Other

C.3. Therapy dates (if unknown, give duration) (mo/day/yr) (Suspect #1)

04/??/1999 to 05/??/1999 Duration: 1 month

C.3. Therapy dates (if unknown, give duration) (mo/day/yr) (Suspect #2)

06/??/1999 to Unknown Duration: 2 months

APR 11 2000

APR 12 2000

MedWatch Forms

(USA)

Patient Number 4

Individual Safety Report

3344035-9-00-01

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

rion Roussel, Inc.

Domain Facsimile — Approved by FDA on 3/22/94

Mfr report # 199920773HMRI

UF/Dist report #

FDA Use Only

A. Patient information

1. Patient identifier	2. Age at time of event:	3. Sex	4. Weight
in confidence	55 yrs Date of birth: 04/02/1944	☒ male	lbs or kgs

B. Adverse event or product problem

1. ☒ Adverse event and/or ☐ Product problem (e.g., defects/malfunctions)

2. Outcomes attributed to adverse event (check all that apply)
- ☐ death
- ☐ life-threatening
- ☒ hospitalization - initial or prolonged
- ☐ disability
- ☐ congenital anomaly
- ☐ required intervention to prevent permanent impairment/damage
- ☐ other:

3. Date of event: 06/28/1999

4. Date of this report: 09/02/1999

5. Describe event or problem

Event (Nature of Event) — Dx Origin

(Dx) LIVER FAILURE — Reporter
(Sx) ASCITES
(Sx) JAUNDICE
(Sx) ENCEPHALOPATHY
(Sx) INCREASED PT NOS
(Sx) INCREASED PTT NOS
(Sx) INCREASED INR NOS
(Sx) ELEVATED LIVER ENZYMES NOS
(Sx) RESPIRATORY DECOMPENSATION

Narrative: Initial report: This postmarketing case from the US was received from a physician and involves a 55 year old male patient who received Arava (leflunomide) unknown dose for rheumatoid arthritis. Specific therapy dates are not known *

6. Relevant tests/laboratory data, including dates

7. Other relevant history, including preexisting medical conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)

ALCOHOL DEPENDENCY, alcohol use

RECEIVED
SEP 0 8 1999
BY:

C. Suspect medication(s)

1. Name (give labeled strength & mfr/labeler, if known)

#1 LEFLUNOMIDE (ARAVA) Tablet

#2

2. Dose, frequency & route used

#1 QD PO

#2

3. Therapy dates (if unknown, give duration)

#1 *

#2

4. Diagnosis for use (indication)

#1 RHEUAMTOID ARTHRITIS

#2

5. Event abated after use stopped or dose reduced

#1 ☐ yes ☐ no ☒ doesn't apply

#2 ☐ yes ☐ no ☐ doesn't apply

6. Lot # (if known)

#1

#2

7. Exp. date (if known)

#1

#2

8. Event reappeared after reintroduction

#1 ☐ yes ☐ no ☒ doesn't apply

#2 ☐ yes ☐ no ☐ doesn't apply

9. NDC # - for product problems only (if known)

#1

#2

10. Concomitant medical products and therapy dates (exclude treatment of event)

ALLOPURINOL
SULFAMETHOXAZOLE, TRIMETHOPRIM (BACTRIM DS)
AMITRIPTYLINE HYDROCHLORIDE (ELAVIL)
LISINOPRIL *

G. All manufacturers

1. Contact office - name/address (& mfrng site for devices)

Hoechst Marion Roussel, Inc.
10236 Marion Park Drive
Kansas City, MO
64137

2. Phone number: (816)966-5000

3. Report source (check all that apply)
- ☐ foreign
- ☐ study
- ☐ literature
- ☐ consumer
- ☒ health professional
- ☐ user facility
- ☐ company representative
- ☐ distributor
- ☐ other:

4. Date received by manufacturer: 08/24/1999

5. (A)NDA # 20-905
IND #
PLA #
pre-1938 ☐ yes
OTC product ☐ yes

6. If IND, protocol #

7. Type of report (check all that apply)
- ☐ 5-day ☒ 15-day
- ☐ 10-day ☐ periodic
- ☒ Initial ☐ follow-up #

8. Adverse event term(s)

LIVER FAILURE, ASCITES, JAUNDICE, ENCEPHALOPATHY, PROTHROMBIN DECREASED, THROMBOPLASTIN DECREASED, PROTHROMBIN DECREASED, LIVER FUNCTION TEST ABNORMAL, *

9. Mfr. report number: 199920773HMRI

E. Initial reporter

1. Name, address & phone *

Warren Alexander MD
Oklahoma City VA Medical Center
Medical Intensive Care Unit
921 NE 13th Streer *

DSS
SEP 0 9 1999

2. Health professional?	3. Occupation	4. Initial reporter also sent report to FDA
☐ yes ☐ no		☐ yes ☐ no ☐ unk

FDA

Domain Facsimile of FDA Form 3500A

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

* Item completed on continuation pages.

B.5. Describe event or problem

[continuation:] however therapy was approximately 2 months duration. It is not indicated if the patient received a loading dose. Significant medical history includes alcohol dependency. Concomitant medications include allopurinol, co-trimoxazole, amitriptyline, lisinopril, fractionated heparin, prednisone, triamcinolone, and verapamil. The reporter states that on 28-Jun-99 the patient was hospitalized with increased PT, increased PTT, increased INR, ascites, jaundice, respiratory decompensation, elevated liver enzymes, encephalopathy, and liver failure. Leflunomide was discontinued on the date of admission to the hospital. The patient has received a total of 18 doses of cholestyramine, although it was not started until 2 weeks into the patient's hospitalization and therapy was not completed due to the extent of the patient's illness. The patient was intubated however, was extubated on 23-Aug-99. As of this report the patient's liver enzymes are still elevated (NOS). The reporter did not provide an assessment of causal relationship. No other information was received at the time of this report.

Reporter assessment of the causal relationship between the adverse event and suspect drug:
[_] Possible [_] Unlikely [_] Unrelated
[_] Insufficient Data
If unlikely/unrelated, provide alternative explanation:
[_] Illness [_] Concomitant Drug [_] Other

C.3. Therapy dates (if unknown, give duration) (mo/day/yr) (Suspect #1)

Unknown to 06/28/1999 Duration: 2 months

C.10. Concomitant medical products and therapy dates (exclude treatment of event)

[continuation:] HEPARIN-FRACTION, SODIUM SALT (LOVENOX)
PREDNISONE
PREDNISONE
TRIAMCINOLONE
VERAPAMIL

G.8. Adverse event term(s)

[continuation:] APNEA

E.1. Name, address & phone #

[continuation:] Oklahoma City, OK
UNITED STATES

MedWatch Forms

(USA)

Patient Number 5

Individual Safety Report

3242747-9-00-01

MED WATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Hoechst Marion Roussel, Inc.

Approved by FDA on 3/22/94

Mfr report # 199813621HMRI

UF/Dist report #

FDA Use Only

A. Patient information

1. Patient identifier	2. Age at time of event:	3. Sex	4. Weight
in confidence	55 yrs or Date of birth: UNK	☒ female ☐ male	____ lbs or ____ kgs

B. Adverse event or product problem

1. ☒ Adverse event and/or ☐ Product problem (e.g., defects/malfunctions)

2. Outcomes attributed to adverse event (check all that apply)

- ☒ death 12/29/1998 (m/d/y/yr)
- ☐ life-threatening
- ☐ hospitalization - initial or prolonged
- ☐ disability
- ☐ congenital anomaly
- ☐ required intervention to prevent permanent impairment/damage
- ☒ other: *

3. Date of event (m/d/y/yr)

4. Date of this report (m/d/y/yr) 04/14/1999

5. Describe event or problem

Event (Nature of Event)	Dx Origin
(Dx) JAUNDICE (FATAL OUTCOME)	Reporter
(Sx) BILIRUBIN 22 (NOS)	
(Dx) ELEVATED LIVER ENZYMES (FATAL OUTCOME)	Reporter
(Sx) AST 288	
(Sx) ALT 63	
(Sx) ALKALINE PHOSPHATASE 766	

Narrative: Initial report: This postmarketing case from the US involves a 55 year old female who was receiving leflunomide 100 mg PO daily for three days as a loading dose and then 20 mg PO daily as a maintenance dose for arthritis from 09-Nov-1998 to 13-Nov-1998. Significant medical history is not mentioned. Concomitant medications include *

6. Relevant tests/laboratory data, including dates

DSS

APR 2 0 1999

ADVERSE EVENT REPORTING SYSTEM

7. Other relevant history, including preexisting medical conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)

HISTORY OF ALCOHOL ABUSE, alcohol use
UNK
UNK
UNK
UNK *

RECEIVED

APR 1 9 1999

BY:

C. Suspect medication(s)

1. Name (give labeled strength & mfr/labeler, if known)

#1 LEFLUNOMIDE (ARAVA) Tablets

#2 LEFLUNOMIDE (ARAVA) Tablets

2. Dose, frequency & route used	3. Therapy dates (if unknown, give duration) (mm/dd/yy (or best estimate))
#1 100 MG/DAY PO	#1 *
#2 20 MG/DAY PO	#2 *

4. Diagnosis for use (indication)	5. Event abated after use stopped or dose reduced
#1 ARTHRITIS	#1 ☐ yes ☒ no ☐ doesn't apply
#2 ARTHRITIS	#2 ☐ yes ☒ no ☐ doesn't apply

6. Lot # (if known)	7. Exp. date (if known)	8. Event reappeared after reintroduction
#1	#1	#1 ☐ yes ☐ no ☒ doesn't apply
#2	#2	#2 ☐ yes ☐ no ☒ doesn't apply

9. NDC # - for product problems only (if known)

#1 #2

10. Concomitant medical products and therapy dates (exclude treatment of event)

LEVOTHYROXINE SODIUM (SYNTHROID)
HYDROXYCHLOROQUINE PHOSPHATE (PLAQUENIL)
NAPROXEN (NAPROSYN)
PROPRANOLOL HYDROCHLORIDE (INDERAL) *

G. All manufacturers

1. Contact office - name/address (& mfrng site for devices)

Hoechst Marion Roussel, Inc.
10236 Marion Park Drive
Kansas City, MO
64137

2. Phone number (816) 966-5000

3. Report source (check all that apply)

- ☐ foreign
- ☐ study
- ☐ literature
- ☐ consumer
- ☒ health professional
- ☐ user facility
- ☐ company representative
- ☐ distributor
- ☐ other:

4. Date received by manufacturer (m/d/y/yr) 04/06/1999

5. (A)NDA # 20-905
IND #
PLA #
pre-1938 ☐ yes
OTC product ☐ yes

6. If IND, protocol #

7. Type of report (check all that apply)

- ☐ 5-day ☒ 15-day
- ☐ 10-day ☐ periodic
- ☐ Initial ☒ follow-up # 1

8. Adverse event term(s)

JAUNDICE, BILIRUBINEMIA, LIVER FUNCTION TEST ABNORMAL, SGOT INCREASED, SGPT INCREASED, ALKALINE PHOSPHATASE INCREASED

9. Mfr. report number

199813621HMRI

E. Initial reporter

1. Name, address & phone #

E.MICHAEL THELEN DR
UNITED STATES 916-966-2067

2. Health professional?	3. Occupation	4. Initial reporter also sent report to FDA
☒ yes ☐ no		☐ yes ☐ no ☐ unk

FDA

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

* Item completed on continuation pages.

Formerly FDA Form 1500A

B.2. Other outcome

medically important

B.5. Describe event or problem

[continuation:] Synthroid (levothyroxine sodium), Plaquenil (hydroxychloroquine phosphate), Naprosyn (naproxen), Inderal (propranolol hydrochloride), and Premarin (estrogens conjugated). The patient experienced jaundice and was evaluated by her physician and studies revealed : bilirubin 22, AST 288, ALT 63, and alkaline phosphatase 766. The hepatitis profile was negative. The event is ongoing at the time of this report. The physician feels the leflunomide was related to the jaundice and the elevated enzymes. The reporter's assessment of the causal relationship is that it cannot be excluded.

Addendum 06-Apr-1999: The physician returned the MedWatch form with this additional information: outcome attributed to adverse event: death 29-Dec-98; relevant medical history: history of alcohol abuse. No other additional information provided.

Event	Serious	Dechal	Rechal	Rpt.Causality	Alternative Explanation
(Dx) JAUNDICE (FATAL OUTCOME)	YES	NO	NA	Possible	underlying/concomitant illness
(Dx) BILIRUBIN 22 (NOS)					
(Dx) ELEVATED LIVER ENZYMES (FATAL OUTCOME)	YES	NO	NA	Possible	underlying/concomitant illness
(Sx) AST 288					
(Sx) ALT 63					
(Sx) ALKALINE PHOSPHATASE 766					

B.7. Other relevant history, including preexisting medical conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)

[continuation:] UNK

C.3. Therapy dates (if unknown, give duration) (mo/day/yr) (Suspect #1)

11/09/1998 to 11/11/1998 Duration: 3 days

C.3. Therapy dates (if unknown, give duration) (mo/day/yr) (Suspect #2)

11/12/1998 to 11/13/1998 Duration: 2 days

C.10. Concomitant medical products and therapy dates (exclude treatment of event)

[continuation:] ESTROGENS CONJUGATED (PREMARIN)

MedWatch Forms

(USA)

Patient Number 6

Individual Safety Report

3469221-9-00-01

Aventis Pharma, Inc.

Domain Facsmile — Approved by FDA on 3/22/94

Mfr report # 200010080HMRI

UF/Dist report #

FDA Use Only

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Patient information

1. Patient identifier	2. Age at time of event:	3. Sex	4. Weight
TG	61 yrs	☐ female	_____ lbs
in confidence	or _____	☒ male	or
	Date of birth: UNK		_____ kgs

B. Adverse event or product problem

1. ☒ Adverse event and/or ☐ Product problem (e.g., defects/malfunctions)

2. Outcomes attributed to adverse event (check all that apply)

- ☐ death _____ (mo/day/yr)
- ☐ life-threatening
- ☒ hospitalization - initial or prolonged
- ☐ disability
- ☐ congenital anomaly
- ☐ required intervention to prevent permanent impairment/damage
- ☐ other: _____

3. Date of event (mo/day/yr): 12/30/1999

4. Date of this report (mo/day/yr): 03/01/2000

5. Describe event or problem

Event (Nature of Event)	Dx Origin
(Dx) ELEVATED LIVER ENZYMES	Reporter
(Dx) LETHARGY	Reporter
(Dx) CONFUSION	Reporter
(Dx) RESPIRATORY FAILURE	Reporter

Narrative: Initial Report: this postmarketing case, received by a pharmacist, involves a 61 year old male who was receiving Arava (leflunomide) for treatment of rheumatoid arthritis (doses and treatment dates not provided). Significant medical history includes anxiety, benign prostatic hyperplasia, cataract, hypertension, rheumatoid arthritis and no known drug allergies. Relevant concomitant medications were atenolol, Halcion (triazolam) *

6. Relevant tests/laboratory data, including dates

MAR 0 6 2000

7. Other relevant history, including preexisting medical conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)

CATARACT
ANXIETY, BENIGNE PROSTATE HYPERPLASIA, HYPERTENSION, RHEUMATOID ARTHRITIS, NO KNOWN DRUG ALLERGIES

C. Suspect medication(s)

1. Name (give labeled strength & mfr/labeler, if known)

#1 LEFLUNOMIDE (ARAVA) Tablets

#2 METHOTREXATE Solution NOS

2. Dose, frequency & route used	3. Therapy dates (if unknown, give duration)
#1 10 MG BID PO	#1
#2	#2

4. Diagnosis for use (indication)

#1 RHEUMATOID ARTHRITIS

#2

5. Event abated after use stopped or dose reduced

#1 ☒ yes ☐ no ☐ doesn't apply

#2 ☐ yes ☐ no ☐ doesn't apply

6. Lot # (if known)	7. Exp. date (if known)
#1	#1
#2	#2

8. Event reappeared after reintroduction

#1 ☐ yes ☐ no ☒ doesn't apply

#2 ☐ yes ☐ no ☐ doesn't apply

9. NDC # - for product problems only (if known)

#1 #2

10. Concomitant medical products and therapy dates (exclude treatment of event)

ATENOLOL
TRIAZOLAM (HALCION)
VERAPAMIL HYDROCHLORIDE (VERAPAMIL - SLOW RELEASE)
ALPRAZOLAM (XANAX)

G. All manufacturers

1. Contact office - name/address (& mfring site for devices)

Aventis Pharma, Inc.
10236 Marion Park Drive
Kansas City, MO
64137

MAR 0 3 2000

2. Phone number: (816) 966-5000

3. Report source (check all that apply)

- ☐ foreign
- ☐ study
- ☐ literature
- ☐ consumer
- ☒ health professional
- ☐ user facility
- ☐ company representative
- ☐ distributor
- ☐ other:

4. Date received by manufacturer (mo/day/yr): 02/25/2000

5. (A)NDA # 20-905

IND # _____

PLA # _____

pre-1938 ☐ yes

OTC product ☐ yes

6. If IND, protocol #

7. Type of report (check all that apply)

- ☐ 5-day ☒ 15-day
- ☐ 10-day ☐ periodic
- ☐ Initial ☒ follow-up # 1

8. Adverse event term(s)

LIVER FUNCTION TEST ABNORMAL, SOMNOLENCE, CONFUSION, APNEA

9. Mfr. report number

200010080HMRI

E. Initial reporter

1. Name, address & phone #

JENNIFER BIU Ms.
HACKENSACK UNIVERSITY MEDICAL CENTER, PHARMACY SERVICES,
30 PROSPECT AVE.
HACKENSACK, NJ 07601 *

2. Health professional?	3. Occupation	4. Initial reporter also sent report to FDA
☒ yes ☐ no		☐ yes ☐ no ☐ unk

FDA

Domain Facsmile of FDA Form 3500A

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

* Item completed on continuation pages.

B.5. Describe event or problem

[continuation:] methotrexate injections, verapamil hydrochloride and Xanax (alprazolam). On 30-Dec-1999 he presented to the emergency department with elevated liver enzymes, lethargy, confusion, and respiratory failure. The patient was placed on a ventilator and admitted to the Coronary Intensive Care Unit. Questran (cholestyramine) was started, following the reccomended dosing for washout, on 01-Jan-2000. The outcome was listed as improving, no further information was available at the time of this report. Additional information will be provided upon receipt.

Laboratory data:	30-Dec am	30-Dec pm	04-Jan
LDH	16,376	3009	
AST	4600	2587	74
ALT		2215	422
tot. Bili		1.2	
dir. Bili		0.87	
Alk. Phos.		123	128

Addednum 25-Feb-2000: The reporting pharmacist returned the MedWatch with the following additional information: the dosing of leflunomide was 10 mg twice a day. The patient was in the Medical Intensive Care Unit and not the Coronary Intensive Care Unit. The cholestyramine was dosed at 8 grams every 8 hours for 11 days. AST was noted to be 4595 on 30-Dec-99 in the morning and not 4600 and the total bilirubin was 1.2 on 04-Jan-2000. No further additional information was received.

Reporter assessment of the causal relationship between the adverse event and suspect drug:
[_] Possible [_] Unlikely [_] Unrelated
[_] Insufficient Data
unlikely/unrelated, provide alternative explanation:
Illness [_] Concomitant Drug [_] Other

MAR 03 2000

E.1. Name, address & phone #

[continuation:] UNITED STATES 201-996-2583

MAR 06 2000

MedWatch Forms

(USA)

Patient Number 7

3862570-1-00-01

...armaceuticals, Inc.

Domain Facsimile — Approved by FDA on 3/22/94

Mfr report # 200123598US

UF/Dist report #

FDA Use Only

MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

A. Patient information

1. Patient identifier: JP in confidence
2. Age at time of event: 66 yrs (or Date of birth: 05/28/1935)
3. Sex: ☐ female ☒ male
4. Weight: ____ lbs (or 95 kgs)

B. Adverse event or product problem

1. ☒ Adverse event and/or ☐ Product problem (e.g., defects/malfunctions)

2. Outcomes attributed to adverse event (check all that apply)
- ☐ death (mo/day/yr)
- ☒ life-threatening
- ☒ hospitalization - initial or prolonged
- ☐ disability
- ☐ congenital anomaly
- ☐ required intervention to prevent permanent impairment/damage
- ☐ other:

3. Date of event (mo/day/yr): 12/??/2001

4. Date of this report (mo/day/yr): 01/28/2002

5. Describe event or problem

Event (Nature of Event)	Dx Origin
(Dx) RENAL FAILURE	Reporter
(Sx) CREATININE (2.2-8.4)	
(Dx) LIVER FAILURE	Reporter
(Dx) THROMBOCYTOPENIA	Reporter
(Dx) GANGRENOUS FINGERS AND TOES	Reporter

Narrative: Initial report: This spontaneous postmarketing case, received from a physician and an intensive care nurse, involves a 66 year old male who initiated therapy with Arava (leflunomide) 20mg daily in late Aug-2001 for rheumatoid arthritis. No loading dose was given. The patient was admitted to the hospital on 13-Dec-2001 for renal and liver failure and thrombocytopenia. The patient also developed gangrenous fingers and toes and *

6. Relevant tests/laboratory data, including dates

7. Other relevant history, including preexisting medical conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)

VIRAL ILLNESS, SMOKER, nicotine use
RHEUMATOID ARTHRITIS

C. Suspect medication(s)

1. Name (give labeled strength & mfr/labeler, if known)
#1 LEFLUNOMIDE (ARAVA) Tablets
#2

2. Dose, frequency & route used
#1 20 MG QD PO
#2

3. Therapy dates (if not known, give duration) (mo/day/yr or best estimate)
#1
#2

4. Diagnosis for use (indication)
#1 RHEUMATOID ARTHRITIS
#2

5. Event abated after use stopped or dose reduced
#1 ☐ yes ☐ no ☐ doesn't apply
#2 ☐ yes ☐ no ☐ doesn't apply

6. Lot # (if known)
#1 UNK
#2

7. Exp. date (if known)
#1
#2

8. Event reappeared after reintroduction
#1 ☐ yes ☐ no ☐ doesn't apply
#2 ☐ yes ☐ no ☐ doesn't apply

9. NDC # - for product problems only (if known)
#1
#2

10. Concomitant medical products and therapy dates (exclude treatment of event)
METHOTREXATE
ROFECOXIB (VIOXX)
PREDNISONE
CALCIUM *

G. All manufacturers

1. Contact office - name/address (& mfring site for devices)
Aventis Pharmaceuticals, Inc.
300 Somerset Corporate Blvd.
Bridgewater, NJ
08807-2854

2. Phone number: (908)243-6000

3. Report source (check all that apply)
- ☐ foreign
- ☐ study
- ☐ literature
- ☐ consumer
- ☒ health professional
- ☐ user facility
- ☐ company representative
- ☐ distributor
- ☐ other:

4. Date received by manufacturer (mo/day/yr): 01/14/2002

5. (A)NDA # 20-905
IND # ____
PLA # ____
pre-1938 ☐ yes
OTC product ☐ yes

6. If IND, protocol #

7. Type of report (check all that apply)
- ☐ 5-day ☒ 15-day
- ☐ 10-day ☐ periodic
- ☐ Initial ☒ follow-up # 1

8. Adverse event term(s)
RENAL FAILURE NOS, BLOOD CREATININE INCREASED, HEPATIC FAILURE, THROMBOCYTOPENIA, GANGRENE NOS

9. Mfr. report number
200123598US

E. Initial reporter

1. Name, address & phone #
ANTHONY SEBBA MD
36338 US HIGHWAY 19 NORTH
PALM HARBOR, FL 34684
UNITED STATES 727-773-9793

2. Health professional? ☒ yes ☐ no

3. Occupation

4. Initial reporter also sent report to FDA ... 01/30/2002 ☐ no ☐ unk

FDA

Domain Facsimile of FDA Form 3500A

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

Item completed on continuation pages

B.5. Describe event or problem

[continuation:] will probably lose his fingertips. The patient began experiencing symptoms about 1 week prior to admission. Leflunomide and methotrexate were discontinued on the day of admission. The events were treated with Questran (cholestyramine) for 2 days, leucovorin, platelets, IV fluids and IVIG for 5 days. The events are resolving, and his labs are improving. His creatinine level decreased from 8.4 to 2.2. No other labs were known at the time of this report. Physician believed that these events could be due to the patient's consumption of oysters which possibly contained "vibro parahaemolyticus" or Salmonella. Concomitant medications include methotrexate, prednisone, Vioxx (rofecoxib), calcium and Centrum (multivitamin). Medical history is significant for a recent viral illness, rheumatoid arthritis, and he is a smoker.

Reporter's assessment of causal relationship: Possible.

Addendum for follow up received 14-Jan-2002: Nurse returned transcribed Medwatch form with note that it was reviewed and was OK. No additional infomation provided.

Addendum for follow-up received 17-Jan-2002: Patient's date of birth and weight provided.

Event	Serious	Dechal	Rechal	Rpt.Causality	Alternative Explanation
(Dx) RENAL FAILURE	YES	NA	NA	Possible	other known or suspected cause
(Sx) CREATININE (2.2-8.4)					
(Dx) LIVER FAILURE	YES	NA	NA	Possible	other known or suspected cause
(Dx) THROMBOCYTOPENIA	YES	NA	NA	Possible	other known or suspected cause
(Dx) GANGRENOUS FINGERS AND TOES	YES	NA	NA	Possible	other known or suspected cause

C.3. Therapy dates (if unknown, give duration) (mo/day/yr) (Suspect #1)

08/??/2001 to 12/13/2001 Duration: 4 months

C.10. Concomitant medical products and therapy dates (exclude treatment of event)

[continuation:] VITAMINS NOS, MINERALS NOS (CENTRUM)

MedWatch Forms

(USA)

Patient Number 8

Individual Safety Report

3651385-5-00-01

Aventis Pharma, Inc.

Approved by FDA on 3/22/94

MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Page 1 of 3

Domain Facsimile
Mfr report # 20002267OUS
UF/Dis report #
FDA Use Only

A. Patient information

1. Patient identifier: MM or In confidence
2. Age at time of event: 66 yrs
   Date of birth: 04/05/1934
3. Sex: female / male
4. Weight: ____ lbs or ____ kgs

B. Adverse event or product problem

1. Adverse event and/or Product problem (e.g., defects/malfunctions)
2. Outcomes attributed to adverse event (check all that apply)
   death: Unknown
   life-threatening
   hospitalization - initial or prolonged
   disability
   congenital anomaly
   required intervention to prevent permanent impairment/damage
   other: *
3. Date of event: 12/21/2000
4. Date of this report: 01/17/2001
5. Describe event or problem

Event (Nature of Event)	Dx Origin
(Dx) LIVER FUNCTION TESTS CONSISTENT W/ MASSIVE HEPATIC NECROSIS	Reporter
(Dx) DISSEMINATED INTRAVASCULAR COAGULOPATHY	Reporter
(Dx) COOMBS TEST POSITIVE NOS	Reporter
(Dx) COLLAPSED AT HOME	Reporter
(Dx) DIARRHEA WITH BLEEDING	Reporter
(Dx) STATUS POST CARDIOPULMONARY ARREST	Reporter
(Dx) METABOLIC ACIDOSIS	Reporter
(Dx) ACUTE RENAL FAILURE	Reporter
(Sx) INCREASED CREATININE 3.5	
(Dx) SEPTIC	Reporter
(Dx) DEATH OF UNKNOWN CAUSE	Reporter

Narrative: Initial Report: This *

8. Relevant tests/laboratory data, including dates

7. Other relevant history, including preexisting medical conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)

NO MENTION OF RELEVANT DISEASE

C. Suspect medication(s)

1. Name (give abeled strength & manufacturer if known)
   #1 LEFLUNOMIDE (ARAVA) Tablets
   #2
2. Dose, frequency & route used
   #1 20 MG QD PO
   #2
3. Therapy dates (if unknown, give duration)
   #1 *
   #2
4. Diagnosis for use (indication)
   #1 RHEUMATOID ARTHRITIS
   #2
5. Event abated after use stopped or dose reduced
   #1 yes no doesn't apply
   #2 yes no doesn't apply
6. Lot # (if known)
   #1 UNK
   #2
7. Exp. date (if known)
   #1
   #2
8. Event reappeared after reintroduction
   #1 yes no doesn't apply
   #2 yes no doesn't apply
9. NDC # - for product problems only (if known)
   #1
   #2
10. Concomitant medical products and therapy dates (exclude treatment of event)

IBUPROFEN (MOTRIN)
PREDNISONE
LANSOPRAZOLE (PREVACID) 11/27/2000 to Unknown

G. All manufacturers

1. Contact office - name/address (& mfr site for devices)
   Aventis Pharma, Inc.
   10236 Marion Park Drive
   Kansas City, MO
   64137
2. Phone number: (816) 966-5000
3. Report source (check all that apply)
   foreign
   study
   literature
   consumer
   health professional
   user facility
   company representative
   distributor
   other
4. Date received by manufacturer: 01/10/2001
5. (A)NDA # 20-905
   IND #
   PLA #
   pre-1938 yes
   OTC product yes
6. If IND, protocol #
7. Type of report (check all that apply)
   5-day 15-day
   10-day periodic
   initial follow-up # 1
8. Adverse event term(s)

LIVER FUNCTION TESTS NOS ABNORMAL, DISSEMINATED INTRAVASCULAR COAGULATION, COOMBS DIRECT TEST POSITIVE, COLLAPSE, DIARRHOEA HAEMORRHAGIC, *

9. Mfr. report number: 20002267OUS

E. Initial reporter

1. Name, address & phone #
   James Wade, MD
   CancerCareSpecialist
   2880 N Monroe St.
   *

DSS

JAN 2 2 2001

2. Health professional? yes
3. Occupation: Hematology
4. Initial reporter also sent report to FDA: yes

JAN 1 9 2001

FDA

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

Item completed on continuation pages

B.2. Other outcome

medically important

B.5. Describe event or problem

[continuation:] post-marketing case from the US was received from a lab tech and consulting hematologist. It involves a 66 year-old female who initiated therapy with Arava (leflunomide) 20 mg daily on 01-Dec-00 for rheumatoid arthritis. It is not reported whether the patient received a loading dose. Relevant medical history and concomitant medications were not reported. One week after initiating therapy with Arava, the patient experienced diarrhea. On 22-Dec-00, the patient collapsed at home and was admitted to the hospital. Liver function tests were consistent with massive hepatic necrosis, no values were reported. Lab tests showed disseminated intravascular coagulopathy and positive Coombs test. No values were provided. The patient was treated with charcoal and cholestyramine treatment was to begin today (25-Dec-00). She is currently on a ventilator in the intensive care unit. The primary care physician was contacted, no information was available.

Additional information was received on 27-Dec-00.
The patient's rheumatologist was not aware of her hospitalization. His office notes indicated that Arava 100mg weekly was initiated sometime at the end of November 2000. Laboratory work was to have been performed 2 weeks later but physicican had no laboratory reports. The patient was hospitalized approximately 3 weeks ago for abdominal pain (no other information available). Most recent admission was for cardiac and pulmonary arrest. The patient was resuscitated, intubated and is improving. The treating physicians at the hospital have not informed the rheumatologist or consulted with him.
The patient's primary care physician knew nothing about the patient's hospitalization other than she "had a reaction". Concomitant medications at last office visit on 27-Nov-2000 were ibuprofen, prednisone and lansoprazole.

Idendum for 08-Jan-01: Follow-up information was received from the hematologist and nurse at hospital. The physician provided the patient was status post cardiopulmonary arrest and on a ventilator. Dosage of Arava 20 mg daily since 01-Dec-00 was confirmed. Additional diagnoses provided were severe diarrhea with bleeding, metabolic acidosis, renal failure and receiving hemodialysis. Onset dates for these events were not provided. A nurse at the hospital indicated that the patient died. The date of death and cause of death were not known to her. She reported the patient had become septic, date not provided. Additional, follow-up information is being requested.

Addendum 10-Jan-2001: Follow-up received from the primary physician: The physician last saw the patient on 27-Nov-2000, where her only complaint was an upset stomach. She was prescribed lansoprazole. The leflunomide was started on 01-Dec-2000 by her rheumatologist. After two weeks ~14-Dec-2000, the patient reported to the rheumatologist that she was fine. The patient was admitted to the hospital on 21-Dec-2000 (not 22-Dec-2000 as previously reported) in full renal failure (creatinine 3.5), dehydrated and in cardiopulmonary arrest. The patient was placed on a ventilator. The patient 's liver enzymes were in the thousands, there was possible disseminated intravascular coagulation, the patient had terrible, strange smelling diarrhea, and the physician was unsure if the patient had episodes of paroxysmal atrial fibrillation. Family members gave conflicting reports on the course of events prior to hospitalization. One family member indicated that the patient had diarrhea for 2 weeks, another indicated 2 days. The patient did not report any diarrhea to her physicians. Her status was described as "everything fell apart at 2:00 PM the day before admission" to "she was fine all day". The physician could not understand the discrepancies. The consulting hematologist believed that the leflunomide caused the diarrhea and hepatic necrosis. Autopsy was performed which the results are not yet available with the exception that there was no evidence of coronary artery disease and the liver biopsy was reported to show only fatty liver. The patient had no prior history of renal failure.

Addendum for 11-Jan-01: Follow-up information was received from the rheumatologist. He provided the patient had no history of alcohol use to his knowledge. Arava was initiated sometime in November, 2000. Liver enzymes on 28-Nov-00 were normal, AST/ALT were between 10-20, no units provided. The patient was treated in the past with methotrexate, "a long time ago". The only concomitant medication the physician was aware of was Motrin (ibuprofen). The rheumatologist feels that there in insufficient evidence to make a causal assessment since "she could have come down with a virus". No other information is available to this physician.

DSS

JAN 2 2 200

JAN 1 9 2001

B.5. Describe event or problem

[continuation:]

Event	Serious	Dechal	Rechal	Rpt.Causality	Alternative Explanation
(Dx) LIVER FUNCTION TESTS CONSISTENT W/ MASSIVE HEPATIC NECROSIS	YES	NA	NA	Possible	possibly associated with concomitant drug(s)
(Dx) DISSEMINATED INTRAVASCULAR COAGULOPATHY	YES	NA	NA		underlying/concomitant illness
(Dx) COOMBS TEST POSITIVE NOS	YES	NA	NA		
(Dx) COLLAPSED AT HOME	YES	UNK	UNK		
(Dx) DIARRHEA WITH BLEEDING	YES	UNK	UNK	Possible	possibly associated with concomitant drug(s)
(Dx) STATUS POST CARDIOPULMONARY ARREST	YES	NA	NA		
(Dx) METABOLIC ACIDOSIS	YES	UNK	UNK		underlying/concomitant illness
(Dx) ACUTE RENAL FAILURE	YES	NA	NA		possibly associated with concomitant drug(s)
(Sx) INCREASED CREATININE 3.5 x) SEPTIC	YES	UNK	UNK		possibly associated with concomitant drug(s)
(Dx) DEATH OF UNKNOWN CAUSE	YES	NA	NA		underlying/concomitant illness

C.3. Therapy dates (if unknown give duration) (mm/dd/yr) (Suspect #1)

11/??/2000 to 12/22/2000 Duration: 1 month

G.8. Adverse event term(s)

[continuation:] CARDIO-RESPIRATORY ARREST, METABOLIC ACIDOSIS NOS, RENAL FAILURE ACUTE, BLOOD CREATININE INCREASED, SEPSIS NOS, DEATH NOS

E.1. Name, address & phone #

[continuation:] Decatur, IL 62526-3269
UNITED STATES 217-876-6600

DSS

JAN 2 2 2001

JAN 1 9 2001

MedWatch Forms

(USA)

Patient Number 9

Individual Safety Report

3859484-X-00-01

Aventis Pharmaceuticals, Inc.

Domain | Facsimile

Mfr report # 200210502US

LF/Dist report #

FDA Use Only

Approved by FDA on 3/2/94

A. Patient information

1. Patient identifier	2. Age at time of event:	3. Sex	4. Weight
JMV	67 yrs or	☐ female	_____ lbs or 59.6 kgs
in confidence	Date of birth: 02/12/1934	☐ male	

B. Adverse event or product problem

1. ☒ Adverse event and/or ☐ Product problem (e.g., defects/malfunctions)

2. Outcomes attributed to adverse event (check all that apply)

☐ death — (mo/day/yr)
☐ life-threatening
☐ hospitalization - initial or prolonged
☒ disability
☐ congenital anomaly
☐ required intervention to prevent permanent impairment/damage
☐ other:

3. Date of event (mo/day/yr): 10/??/2001

4. Date of this report (mo/day/yr): 01/22/2002

5. Describe event or problem

Event (Nature of Event)	Dx Origin
(Dx) HEPATIC FAILURE	Reporter
(Sx) JAUNDICE	
(Sx) TOTAL BILIRUBIN 25.1	
(Sx) AST 61	
(Sx) ALKALINE PHOSPHATASE 160	
(Dx) DIARRHEA	Reporter
(Dx) WEAKNESS	Reporter
(Dx) PNEUMONIA	Reporter
(Sx) PULMONARY INFILTRATE	

Narrative: Initial report 16-Jan-2002: This postmarketing case reported by a physician and pharmacists involves a 67-year-old female patient receiving Arava (leflunomide) 20mg once a day for rheumatoid arthritis since September 2001. It is not indicated if the patient received the loading dose *

6. Relevant tests/laboratory data including dates

DSS

7. Other relevant history, including preexisting medical conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)

HYPERTENSION, GASTRITIS, STEROID INDUCED DIABETES, SJOGREN'S SYNDROME, VERTEBRAL BASILAR INSUFFICIENCY, GERD, GRADE III ESOPHAGEAL VARICES PER EGD (12/99 & 09/2001), ALLERGY TO ASPIRIN, ALLERGY TO FELDENE, ALLERGY TO MOTRIN, allergy

DSS

JAN 25

C. Suspect medication(s)

1. Name (give labeled strength & mfr/labeler, if known)

#1 LEFLUNOMIDE (ARAVA) Tablets

#2

2. Dose, frequency & route used

#1 20 MG QD PO

#2

3. Therapy dates (if unknown, give duration) (mo/day/yr or best estimate)

#1 *

#2

4. Diagnosis for use (indication)

#1 RHEUMATOID ARTHRITIS

#2

5. Event abated after use stopped or dose reduced

#1 yes no doesn't apply

#2 yes no doesn't apply

6. Lot # (if known)

#1 UNK

#2

7. Exp. date (if known)

#1

#2

8. Event reappeared after reintroduction

#1 yes no doesn't apply

#2 yes no doesn't apply

9. NDC # - for product problems only (if known)

#1

#2

10. Concomitant medical products and therapy dates (exclude treatment of event)

UNKNOWN DRUG (UNKNOWN DRUG)

G. All manufacturers

1. Contact office - name/address (& mfr/lic site for devices)

Aventis Pharmaceuticals, Inc.
300 Somerset Corporate Blvd.
Bridgewater, NJ
08807-2854

2. Phone number: (908)243-5000

3. Report source (check all that apply)

☐ foreign
☐ study
☐ literature
☐ consumer
☐ health professional
☐ user facility
☐ company representative
☐ distributor
☐ other

4. Date received by manufacturer (mo/day/yr): 01/16/2002

5. (A)NDA # 20-905
IND #
PLA #
pre-1938 yes
OTC product yes

6. If IND, protocol #

7. Type of report (check all that apply)

☐ 5-day ☒ 15-day
☐ 10-day ☐ periodic
☐ initial ☐ follow-up #

8. Adverse event term(s)

HEPATIC FAILURE, JAUNDICE NOS, BLOOD BILIRUBIN INCREASED, ASPARTATE AMINOTRANSFERASE INCREASED, BLOOD ALKALINE PHOSPHATASE NOS INCREASED *

9. Mfr. report number

200210502US

E. Initial reporter

1. Name, address & phone #

GISELE BOURONCLE MD
153 CONCORD ST.
ST. PAUL, MN 55107
UNITED STATES 651-602-7554

2. Health professional? yes no

3. Occupation

4. Initial reporter also sent report to FDA yes no

FDA

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

Item completed on continuation pages

JAN 24 2002

Aventis Pharmaceuticals, Inc.

MED WATCH	A.1. Patient Identifier	G.9. Mfr. report number
	JMV	200210502US

B.5. Describe event or problem

[continuation:] of leflunomide. Relevant medical history includes hypertension, gastritis, steroid induced diabetes, grade III esophageal varices (unknown etiology and unknown what further workup was performed) per EGD in 12/99 & 09/01, and allergies to aspirin, Feldene (piroxicam), and Motrin (ibuprofen). She has taken Imuran (azathioprine) and methotrexate in the past. She takes many concomitant medications (nos). Patient was seen by her primary care physician (reporter) on 16-Dec-2001 when she presented with yellow skin color. At this time, her total bilirubin was 9.5, AST 48, ALT 27, and alkaline phosphatase 160. She was diagnosed with jaundice. Arava was discontinued on ~25-Dec-2001. On 03-Jan-2002, the patient presented to the hospital with pulmonary infiltrates and jaundice. Her total bilirubin was increased to 19 at this time. She was treated for pneumonia and had further workup for liver disease (multiple labs) and liver biopsy. She was discharged on 11-Jan-2002. On 14-Jan-2002, she presented to a different hospital with diarrhea, weakness, and jaundice. Liver biopsy results (January 2002) showed "fibrosis and marked canalicular cholestasis suggestive of possible medication reaction". She was started on Questran (cholestyramine) 8 gram by mouth every 8 hours to "increase in the elimination of Arava" (January 2002 Her abdominal CT from December 2001 shows "hepatic cirrhosis with varices". The events are ongoing. Arava was prescribed by the patient's rheumatologist. She is currently being worked up for a liver transplant. Onset date of the above event: ~October 2001.
Her labs are as follows:
14-Jan-2002: INR--1.5, NH3--47, total bilirubin--25.1, AST--61, ALT--31, alkaline phosphatase--151
15-Jan-2002: INR--1.5, NH3--75, total bilirubin--21.2, AST--59, ALT--29, alkaline phosphatase--145
16-Jan-2002: INR--1.5, NH3--83, total bilirubin--20.7, AST--59, ALT--28, alkaline phosphatase--132
No additional information was provided.

The reporter's causal assessment between Arava and the events are unknown.

Reporter assessment of the causal relationship between the adverse event and suspect drug:
[_] Possible [_] Unlikely [_] Unrelated
[_] Insufficient Data
If unlikely/unrelated, provide alternative explanation:
[_] Illness [_] Concomitant Drug [_] Other

C.3. Therapy dates (if unknown give duration) (mo/day/yr) (Suspect #1)

09/??/2001 to 12/25/2001 Duration: 3 months

G.8. Adverse event term(s)

[continuation:] DIARRHOEA NOS, WEAKNESS, PNEUMONIA NOS, LUNG INFILTRATION NOS

3867296-6-00-01

MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

For VOLUNTARY reporting by health professionals of adverse events and product problems

CDER

Page — of —

Form Approved: OMB No. 0910-0291 Expires: 12/31/00 See OMB statement on reverse.

FDA Use Only (MDR#)

Triage unit

FDA # 161239

A. Patient information

1. Patient identifier: JMV (In confidence)
2. Age at time of event: 67 or Date of birth: 2/12/34
3. Sex: ☒ female ☐ male
4. Weight: 131 lbs or 59.6 kgs

B. Adverse event or product problem

1. ☒ Adverse event and/or ☐ Product problem (e.g., defects/malfunctions)

2. Outcomes attributed to adverse event (check all that apply)
☐ death _____ (mo/day/yr)
☒ life-threatening
☒ hospitalization – initial or prolonged
☒ disability
☐ congenital anomaly
☐ required intervention to prevent permanent impairment/damage
☐ other: _____

3. Date of event (mo/day/yr): ~ 9/01
4. Date of this report (mo/day/yr): 1/17/2002

5. Describe event or problem
12/99 + EGD showed Grade III Esophageal varicies - unknown etiology - unknown what further workup was performed. Arava started approx 9/01. Presented to hospital 1/3/02 c pulm infiltrates - jaundice, ? T.bili (19). Treated for pneumonia - further workup of liver disease (multiple labs) + liver biopsy. Discharged 1/11/02. Presented to a different hospital 1/14/02 c diarrhea, weakness + jaundice. Liver biopsy results obtained, symptomatic Rx (antidiarrheals) + Questran started to increase elimination of Arava
12/01 Abdomen CT: hepatic cirrhosis c varices

6. Relevant tests/laboratory data, including dates

1/14/02:	1/15/02:	1/16/02:
INR = 1.5	INR = 1.5	INR = 1.5
NH_3 = 47	NH_3 = 75	NH_3 = 83
T.bili = 25.1	T.bili = 21.2	T.bili = 20.7
AST = 61	AST = 59	AST = 59
ALT = 31	ALT = 29	ALT = 28
Alkphos = 151	Alkphos = 145	Alkphos = 132

1/02 Liver biopsy: Fibrosis + marked canalicular cholestasis suggestive of possible med reaction

7. Other relevant history, including preexisting medical conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)
HTN
Rheumatoid Arthritis
Sjogrens Syndrome
GERD
Steroid induced glucose intolerance
Vertebral basilar insufficiency
Previous use of Imuran + MTX (? dates)

C. Suspect medication(s)

1. Name (give labeled strength & mfr/labeler, if known)
#1 Leflunomide (Arava) 20 mg
#2

2. Dose, frequency & route used
#1 20mg po qd
#2

3. Therapy dates (if unknown, give duration)
#1 approx 9/01 – 12/01
#2

4. Diagnosis for use (indication)
#1 Rheumatoid Arthritis
#2

5. Event abated after use stopped or dose reduced
#1 ☐ yes ☒ no ☐ doesn't apply
#2 ☐ yes ☐ no ☐ doesn't apply

6. Lot # (if known)
#1
#2

7. Exp. date (if known)
#1
#2

8. Event reappeared after reintroduction
#1 ☐ yes ☐ no ☒ doesn't apply
#2 ☐ yes ☐ no ☐ doesn't apply

9. NDC # (for product problems only)
- -

10. Concomitant medical products and therapy dates (exclude treatment of event)

D. Suspect medical device

1. Brand name
2. Type of device
3. Manufacturer name & address
4. Operator of device
☐ health professional
☒ lay user/patient
☐ other: _____
5. Expiration date (mo/day/yr)
6. model # _____ catalog # MEDWATCH CTU serial # _____ lot # _____ other # _____
7. If implanted, give date (mo/day/yr)
8. If explanted, give date (mo/day/yr)
9. Device available for evaluation? (Do not send to FDA)
☐ yes ☐ no ☐ returned to manufacturer on _____ (mo/day/yr)
10. Concomitant medical products and therapy dates (exclude treatment of event)

RECEIVED
FEB 08 2002

E. Reporter (see confidentiality section on back)

1. Name, address & phone #
CARRIE WERNER Pharm D
333 N Smith Ave
St Paul MN 55102

2. Health professional? ☒ yes ☐ no
3. Occupation: Pharmacist
4. Also reported to
☐ manufacturer
☐ user facility
☐ distributor

5. If you do NOT want your identity disclosed to the manufacturer, place an "X" in this box. ☒

Mail to: MEDWATCH, 5600 Fishers Lane, Rockville, MD 20852-9787 or FAX to: 1-800-FDA-0178

FDA Form 3500 (6/99) Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

CTV161239 MEDWATCH FEB 08 2002

DSS FEB 1 0 2002

MedWatch Forms

(USA)

Patient Number 10

Individual Safety Report
3720213-1-00-01

)LUNTARY reporting
h professionals of adverse
s and product problems

Form approved: OMB No. 0910-0291 Expires: 9/31/02
See OMB statement on reverse.

FDA Use Only
Triage unit
complaint # 143047

THE FDA MEDI[illegible] PRODUCTS REPORTING PROGRAM

A. Patien[illegible]nformation

1. Patient identif[illegible]
RS
In confidence

2. Age at time of event: 25 years
or
Date of birth: _____

3. Sex
☒ female
☐ male

4. Weight
_____ lbs
or
_____ kgs

B. Adver[illegible]event or product problem

1. ☒ Adverse [illegible]nt and/or ☐ Product problem (e.g., defects/malfunctions)

2. Outcomes att[illegible]ted to adverse event (check all that [illegible]ly)
☐ death _____ (mm/dd/yyyy)
☐ life-threat[illegible]g
☒ hospitaliz[illegible]n – initial or prolonged
☐ disability
☐ congenital anomaly
☐ required intervention to prevent permanent impairment/damage
☐ other: _____

3. Date of event (mm/dd/yyyy): [illegible]/12/1999

4. Date of this report (mm/dd/yyyy): 4/24/2000

5. Describe eve[illegible]or problem

Pt admitted 2° ↑LFT's, MS Δ's
possib[illegible] 2° amiodarone + leflunomide. Meds discontinued
Pt admitted. Less confused
+ MS improved

6. Relevant testi[illegible]boratory data, including dates

6/7 – Follow-up
INFO –

7. Other relevan[illegible]story, including preexisting medical conditions (e.g., allergies, re[illegible]pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)

Hepatitis C 2° transfusion
HTN, CA, OA, Afib, CHF

CTU 143047

C. Suspect medication(s)

1. Name (Product Name) (Labeled Strength) (Mfr/Labeler)
#1 Amiodarone / _____
#2 Leflunomide / _____

2. Dose/Frequency/Route used
#1 / /
#2 / /

3. Therapy dates (if unknown, give duration)
From To (or best estimate)
#1 _____ – _____
#2 _____ –

4. Diagnosis for use (separate indications with comma's)
#1
#2

5. Event abated after use stopped or dose reduced
#1 ☐ yes ☐ no ☐ doesn't apply
#2 ☐ yes ☐ no ☐ doesn't apply

6. Lot # (if known)
#1
#2

7. Exp. date (if known)
#1
#2

8. Event reappeared after reintroduction
#1 ☐ yes ☐ no ☐ doesn't apply
#2 ☐ yes ☐ no ☐ doesn't apply

9. NDC # (for product problems only)
– –

10. Concomitant medical products and therapy dates (exclude treatment of event)

D. Suspect medical device

1. Brand name

2. Type of device

3. Manufacturer name & address

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MAY 10 2001
MEDWATCH CTU

4. Operator of device
☐ health professional
☐ lay user/patient
☐ other

5. Expiration date (mm/dd/yyyy)

6.
model # _____
catalog # _____
serial # _____
lot # _____
other # _____

7. If implanted, give date (mm/dd/yyyy)

8. If explanted, give date (mm/dd/yyyy)

9. Device available for evaluation? (Do not send to FDA)
☐ yes ☐ no ☐ returned to manufacturer on _____ (mm/dd/yyyy)

10. Concomitant medical products and therapy dates (exclude treatment of event)

E. Reporter (see confidentiality section on back)

1. Name
Jamie Pack, Pharm.D
Drug Information Service, Rush Medical Ctr.
1653 W. Congress Parkway
Chicago IL 60612

phone # 312-942-6525

2. Health professional?
☒ yes ☐ no

3. Occupation
Pharmacist

4. Also reported to
☐ manufacturer
☐ user facility
☐ distributor

5. If you do not want your identity disclosed to the manufacturer, place an "X" in this box. ☒

FDA

Mail to: MEDWATCH
5600 Fishers Lane
Rockville, MD 20852-9787

or FAX to:
1-800-FDA-0178

FDA Form 3500 MAY 10 2001

Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

MedWatch Forms

(USA)

Patient Number 11

3892731-7-00-01

MEDWATCH

The FDA Safety Information and Adverse Event Reporting Program

VOLUNTARY reporting of adverse events and product problems

CDER

Form Approved: OMB No. 0910-0291 Expires: 04/30/03
See OMB statement on reverse

FDA Use Only
Triage unit sequence #: 164596

Internet Submission - Page 1 of 3

Faxed to R.B. on mail loss

A. Patient information

1. Patient identifier	2. Age at time of event:	3. Sex	4. Weight
JH	75 Years or Date of birth:	☑ female ☐ male	___ lbs or ___ kgs
In confidence			

B. Adverse event or product problem

1. ☑ Adverse event and/or ☐ Product problem (e.g., defects/malfunctions)

2. Outcomes attributed to adverse event (check all that apply)
- ☑ death 09/12/1999 (mo/day/yr)
- ☐ life-threatening
- ☐ hospitalization - initial or prolonged
- ☐ disability
- ☐ congenital anomaly
- ☐ required intervention to prevent permanent impairment/damage
- ☐ other:

3. Date of event (mo/day/yr): 09/09/1999

4. Date of this report (mo/day/yr): 03/26/2002

5. Describe event or problem

75 y/o female with a 5 year history of rheumatoid arthritis and cutaneous lupu was started on leflunomide in April of 1999. She had laboratories every 6 weeks including LFTs which were normal. She had a known history of atrial fibrillation for which she was treated with Propafenone and coumadin. On 9/9/1999 she was admitted for a fast irregular heart beat. Her heart rate was 150 but was hemodynamically stable. On 9/10/1999 she was converted with electrical cardioversion and given one doe of Amiodarone. Later that morning on 9/10, her laboratories returned and AST = 1186, her ALT = 669 and her Alk Phos = 58. Over the next 2 days she went into progressive liver failure and passed away on 9/12/1999 with the AST = 4682, the ALT = 2202, the Tot Bili = 3 and the Alk Phos = 92. The leflunomide and amiodarone -1 dose only- were stopped and the patient had been

6. Relevant tests/laboratory data, including dates

The creatnine was normally 0.8, but on admission, it was 1.9 and on the day of her death it was 2.6. On admission, the WBC = 5.2, the HCO3 = 20, the BUN = 53, the albumin = 2.5 and the INR = 5.7 -normally 1.6 to 2.0-.

7. Other relevant history, including preexisting medical conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)

There was no history of alcohol intake, hepatitis or exposure to other liver toxins.

MEDWATCH

MAR 29 2002

CDER 164596

C. Suspect medication(s)

1. Name (give labeled strength & mfr/labeler, if known)
- #1 Leflunomide 20 mg Aventis
- #2

2. Dose, frequency & route used
- #1 20 mg day Oral
- #2

3. Therapy dates (if unknown, give duration) (from/to or best estimate)
- #1 04/01/1999 09/09/1999
- #2

4. Diagnosis for use (indication)
- #1 rheumatoid arthritis
- #2

5. Event abated after use stopped or dose reduced
- #1 ☐ yes ☐ no ☑ doesn't apply
- #2 ☐ yes ☐ no ☐ doesn't apply

6. Lot # (if known)
- #1
- #2

7. Exp. date (if known)
- #1
- #2

8. Event reappeared after reintroduction
- #1 ☐ yes ☐ no ☑ doesn't apply
- #2 ☐ yes ☐ no ☐ doesn't apply

9. NDC # (for product problems only)

10. Concomitant medical products and therapy dates (exclude treatment of event)

Accupril 10 mg QD Lasix 40 mg QD
Prilosec 10 mg QD Propafenone 225 mg TID
Premarin 0.625 mg QD Plaquenil 200 mg QD Amio

D. Suspect medical device

1. Brand name

2. Type of device

3. Manufacturer name & address

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MAR 30 2002
MEDWATCH CTU

4. Operator of device
- ☐ health professional
- ☐ lay user/patient
- ☐ other:

5. Expiration date (mo/day/yr)

6. model #
catalog #
serial #
lot #
other #

7. If implanted, give date (mo/day/yr)

8. If explanted, give date (mo/day/yr)

9. Device available for evaluation? (Do not send to FDA)
☐ yes ☐ no ☐ returned to manufacturer on (mo/day/yr)

DSS

MAR 30 2002

10. Concomitant medical products and therapy dates (exclude treatment of event)

E. Reporter (see confidentiality section on back)

1. Name & address

David E. Yocum, MD
Room 8303, 1501 N Campbell Ave
Tucson Arizona 85724
United States yocumau.arizona.edu

phone # 520-626-6399

2. Health professional? ☑ yes ☐ no

3. Occupation: Physician

4. Also reported to
- ☐ manufacturer
- ☐ user facility
- ☐ distributor

5. If you do NOT want your identity disclosed to the manufacturer, place an " X " in this box. ☑

Mail to: MEDWATCH, 5600 Fishers Lane, Rockville, MD 20857-9787 or FAX 1-800-FDA-0178

RECEIVED

FDA Form 3500

Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

3892731-7-00-02

164596

MEDWATCH

For VOLUNTARY reporting by health professionals of adverse events and product problems
Internet Submission - Page 2 of 3

B5. Describe event or problem continued

put on cholestyramine 4 grams TID without effect. Her family refuse an autopsy.

164596

Mail to: MEDWATCH
5600 Fishers Lane
Rockville, MD 20852-9787

or FAX to:
1-800-FDA-0178

C10. Concomitant medical products and therapy dates continued

darone 800mg -one dose-

D10. Concomitant medical products and therapy dates continued

Mail to: MEDWATCH
5600 Fishers Lane
Rockville, MD 20852-9787

or FAX to:
1-800-FDA-0178

MedWatch Forms

(USA)

Patient Number 12

Individual Safety Report

3562186-0-00-01

MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

FOR VOLUNTARY reporting by health professionals of adverse events and product problems

Internet Submission - Page 1 of 2

Form Approved: OMB No. 0910-0291 Expires: 11/30/03
See OMB statement on reverse.

FDA Use Only

Triage unit sequence # 128229

A. Patient information

1. Patient identifier: CI — In confidence

2. Age at time of event: [illegible] years or Date of birth: 08/08/1923

3. Sex: ☑ female ☐ male

4. Weight: ____ lbs or ____ kgs

B. Adverse event or product problem

1. ☑ Adverse event and/or ☐ Product problem (e.g., defects/malfunctions)

2. Outcomes attributed to adverse event (check all that apply)
- ☐ death (mm/dd/yyyy)
- ☑ life-threatening
- ☑ hospitalization - initial or prolonged
- ☐ disability
- ☐ congenital anomaly
- ☑ required intervention to prevent permanent impairment/damage
- ☐ other

3. Date of event: 07/11/2000 (mm/dd/yyyy)

4. Date of this report: 08/30/2000 (mm/dd/yyyy)

5. Describe event or problem

76yof with rheumatoid arthritis receiving prednisone, Arava, Percocet -one tab q4h prn-, and Tylenol -650 mg qid prn- -duration of use of acetaminophen-containing products is unclear- was admitted from outside hospital on 7/11/00 after increasing confusion, BP of 80/50, positive hemocult, ammonia level of 85, AST of > 4500, ALT of 1019, bilirubin of 1.2, alk phos of 195, PT greater than 33, albumin of 2.8, and with a pulse-ox reading of 96%. Patient had no prior history of alcohol use or liver disease. Patient was provided supportive therapy and treated with N-aceytlcysteine and Vitamin K. AST improved to 62, ALT to 78, alkaline phosphatase to 102 by 7/18. Bilirubin peaked at 2.4 and decreased to 1.0 by 7/26/00.

6. Relevant tests/laboratory data, including dates

BP of 80/50, positive hemocult, ammonia level of 85, AST of > 4500. ALT of 1019, bilirubin of 1.2, alk phos of 195, PT greater than 33, albumin of 2.8, and with a pulse-ox reading of 96%. After treatment and discontination of suspect drugs AST improved to 62, ALT to 78, alkaline phosphatase to 102 by 7/18 Bilirubin peaked at 2.4 and decreased to 1.0 by 7/26/00.

7. Other relevant history, including preexisting medical conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)

Past medical history of rheumatoid arthritis, history of osteoarthritis involving the lumbar spine, status postdecompression and fusion of the lumbar spine, history of COPD, history of systemic hypertension, status post right tibial fracture. Past surgical history: arthroplasties of both knees and ORIF

C. Suspect medication(s)

1. Name (Product Name) / (Labeled Strength) / (Mfr/Labeler)
- #1 Arava / 20mg / Hoechst Marion Rousse
- #2 Acetaminophen / [illegible]mg / Unknown

2. Dose/Frequency/Route used
- #1 20mg / daily / Oral
- #2 ~975m g / q 4 to 6 / Oral

3. Therapy dates (if unknown, give duration) From / To (or best estimate)
- #1 07/12/1999 - 07/12/2000
- #2 02/01/2000 - 07/12/2000

4. Diagnosis for use (separate indications with comma)
- #1 Rheumatoid Arthritis
- #2 Pain

5. Event abated after use stopped or dose reduced
- #1 ☑ yes ☐ no ☐ doesn't apply
- #2 ☑ yes ☐ no ☐ doesn't apply

6. Lot # (if known)
- #1
- #2

7. Exp. date (if known)
- #1
- #2

8. Event reappeared after reintroduction
- #1 ☐ yes ☐ no ☑ doesn't apply
- #2 ☐ yes ☐ no ☑ doesn't apply

9. NDC # (for product problems only)
- -
- -

10. Concomitant medical products and therapy dates (exclude treatment of event)

MEDICATIONS ON TRANSFER: Duragesic patch, 50 mg every 72 hours; Calcium carbonate 500 mg p.o. q. day; Magnesium oxide 400 mg

D. Suspect medical device

1. Brand name

2. Type of device

3. Manufacturer name & address

DSS

AUG 31 2000

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AUG 31 2000

MEDWATCH CTU

4. Operator of device
- ☐ health professional
- ☐ lay user/patient
- ☐ other

5. Expiration date (mm/dd/yyyy)

6. model # / catalog # / serial # / lot # / other #

7. If implanted, give date (mm/dd/yyyy)

8. If explanted, give date (mm/dd/yyyy)

9. Device available for evaluation? (Do not send device to FDA)
- ☐ yes ☐ no ☐ returned to manufacturer on (mm/dd/yyyy)

10. Concomitant medical products and therapy dates (exclude treatment of event)

E. Reporter (see confidentiality section on back)

1. Name — phone # 412 624-4987

Peg Verrico, RPh
University of Pittsburgh Medical Center [illegible] Victoria Hall
Pittsburgh Pennsylvania 15261
United States verricopm@msx.upmc.edu

2. Health professional? ☑ yes ☐ no

3. Occupation: Pharmacist

4. Also reported to
- ☐ manufacturer
- ☐ user facility
- ☐ [illegible]

5. If you do not want your identity disclosed to the manufacturer, place an "X" in this box. ☑

FDA

FDA Form 3500

Mail to: MEDWATCH, 5600 Fishers Lane, Rockville, MD 20857-9787

FAX to: 1-800-FDA-0178

Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event

MEDWATCH
THE FDA MEDICAL PRODUCTS REPORTING PROGRAM
HF-2

CTU 128229

128229

MEDWATCH

For VOLUNTARY reporting by health professionals of adverse events and product problems
Internet Submission - Page 5 of 6

C10. Concomitant medical products and therapy dates continued

p.o. q.day; Prednisone 5 mg p.o. q. day; Paxil 40 mg p.o. q. day; Prinivil 5 mg p.o. q. day; Zantac 150 mg p.o. q. day; Colace 1 p.o. b.i.d.

F/U received

D10. Concomitant medical products and therapy dates continued

DSS

AUG 3 1 2000

Mail to: MEDWATCH
5600 Fishers Lane
Rockville, MD 20852-9787
or FAX to 1-800-FDA-0178

Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

128229

MedWatch Forms

(USA)

Patient Number 13

Individual Safety Report

3481613-0-00-01

Aventis Pharma, Inc.

Domain Facsimile — Approved by FDA on 3/22/94

Mfr report # 200010951HMRI

UF/Distr report #

FDA Use Only

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

A. Patient information

1. Patient identifier	2. Age at time of event:	3. Sex	4. Weight
??	or UNK	☐ female	____ lbs
in confidence	Date of birth: UNK	☐ male	or ____ kgs

B. Adverse event or product problem

1. ☒ **Adverse event** and/or ☐ **Product problem** (e.g., defects/malfunctions)

2. Outcomes attributed to adverse event (check all that apply)
- ☒ death 03/01/2000 (mo/day/yr)
- ☐ life-threatening
- ☒ hospitalization - initial or prolonged
- ☐ disability
- ☐ congenital anomaly
- ☐ required intervention to prevent permanent impairment/damage
- ☐ other:

3. Date of event (mo/day/yr): 03/??/2000

4. Date of this report (mo/day/yr): 03/27/2000

5. Describe event or problem

Event (Nature of Event)	Dx Origin
(Dx) NEAR SYNCOPAL EPISODE	Reporter
(Dx) SHOCK (FATAL)	Reporter
(Dx) LIVER FAILURE	Reporter
(Dx) PANCREATITIS	Reporter
(Dx) INTERSTITIAL LUNG DISEASE (FATAL)	Reporter

Narrative: Initial report: This postmarketing case from the US was received from a physician and involves a female patient of unknown age who was receiving leflunomide (Arava) 100 mg orally daily as a 3 day loading dose then 20 mg orally daily for rheumatoid arthritis from Dec-1999 to 01-Mar-2000. Significant medical history includes interstitial lung disease. No *

6. Relevant tests/laboratory data, including dates

7. Other relevant history, including preexisting medical conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)

INTERSTITIAL LUNG DISEASE

DSS

MAR 30 2000

C. Suspect medication(s)

1. Name (give labeled strength & mfr/labeler, if known)
- #1 LEFLUNOMIDE (ARAVA) Tablets
- #2 LEFLUNOMIDE (ARAVA) Tablets

2. Dose, frequency & route used
- #1 100 MG QD PO
- #2 20 MG QD PO

3. Therapy dates (if unknown, give duration) (from/to or best estimate)
- #1 *
- #2 *

4. Diagnosis for use (indication)
- #1 RHEUMATOID ARTHRITIS
- #2 RHEUMATOID ARTHRITIS

5. Event abated after use stopped or dose reduced
- #1 yes no doesn't apply
- #2 yes no doesn't apply

6. Lot # (if known)
- #1 UNK
- #2 UNK

7. Exp. date (if known)
- #1
- #2

8. Event reappeared after reintroduction
- #1 yes no doesn't apply
- #2 yes no doesn't apply

9. NDC # - for product problems only (if known)
- #1
- #2

10. Concomitant medical products and therapy dates (exclude treatment of event)

NO CONCOMITANT DRUG GIVEN

G. All manufacturers

1. Contact office - name/address (& mfr'ing site for devices)

Aventis Pharma, Inc.
10236 Marion Park Drive
Kansas City, MO
64137

2. Phone number: (816) 966-5000

3. Report source (check all that apply)
- ☐ foreign
- ☐ study
- ☐ literature
- ☐ consumer
- ☐ health professional
- ☐ user facility
- ☐ company representative
- ☐ distributor
- ☐ other:

MAR 29 2000

4. Date received by manufacturer (mo/day/yr): 03/16/2000

5. (A)NDA # 20-905
- IND #
- PLA #
- pre-1938 ☐ yes
- OTC product ☐ yes

6. If IND, protocol #

7. Type of report (check all that apply)
- ☐ 5-day ☐ 15-day
- ☐ 10-day ☐ periodic
- ☐ Initial ☐ follow-up #

8. Adverse event term(s)

DIZZINESS, SHOCK, LIVER FAILURE, PANCREATITIS, INTERSTITIAL PNEUMONIA

9. Mfr. report number

200010951HMRI

E. Initial reporter

1. Name, address & phone #

MITCHELL FEINMAN MD
1737 VILLAGE PARK DRIVE
ORANGEBURG, SC 29118
UNITED STATES 803-539-2224

2. Health professional? ☐ yes ☐ no

3. Occupation

4. Initial reporter also sent report to FDA? ☐ yes ☐ no ☐ unk

FDA

Domain Facsimile of FDA Form 3500A

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

* Item completed on continuation pages

B.5. Describe event or problem

[continuation] relevant concomitant medications mentioned. In Mar-2000, the patient presented to the emergency room with a near syncopal episode and shock NOS. The patient was hospitalized with liver failure, pancreatitis, and interstitial lung disease, and subsequently died on 01-Mar-2000. Arava was discontinued upon hospitalization, but the patient did not undergo a washout.
Additional information has been requested and will be forwarded upon receipt.

Reporter's assessment of causal relationship: Cannot be excluded.

Event	Serious	Dechal	Rechal	Rpt.Causality	Alternative Explanation
(Dx) NEAR SYNCOPAL EPISODE	YES	UNK	NA	Possible	
(Dx) SHOCK (FATAL)	YES	UNK	NA	Possible	
(Dx) LIVER FAILURE	YES	UNK	NA	Possible	
(Dx) PANCREATITIS	YES	UNK	NA	Possible	
(Dx) INTERSTITIAL LUNG DISEASE (FATAL)	YES	UNK	NA	Possible	

C.3. Therapy dates (if unknown, give duration) (mo/day/yr) (Suspect #1)

12/??/1999 to 12/??/1999 Duration: 3 days

C.3. Therapy dates (if unknown, give duration) (mo/day/yr) (Suspect #2)

12/??/1999 to 03/??/2000 Duration: 3 months

MAR 29 2000

DSS

MAR 30 2000

MedWatch Forms

(USA)

Patient Number 14

Individual Safety Report

3424801-1-00-01

Hoechst Marion Roussel, Inc.

Page 1 of 2

Domain Facsimile — Approved by FDA on 3/22/94

Mfr report # 199922130HMRI

IND/Dist report #

FDA Use Only

Patient information

1. Patient identifier	2. Age at time of event: UNK or Date of birth:	3. Sex	4. Weight
in confidence		female / male	lbs or kgs

B. Adverse event or product problem

1. [X] Adverse event and/or [ ] Product problem (e.g., defects/malfunctions)

2. Outcomes attributed to adverse event (check all that apply)
- [ ] death — (m/d/y/yr)
- [X] life-threatening
- [ ] hospitalization - initial or prolonged
- [ ] disability
- [ ] congenital anomaly
- [ ] required intervention to prevent permanent impairment/damage
- [ ] other: *

3. Date of event (m/d/y/yr)

4. Date of this report (m/d/y/yr): 12/15/1999

5. Describe event or problem

Event (Nature of Event) — Dx Origin

(Dx) HEPATIC FAILURE — Reporter
(Sx) JAUNDICE
(Sx) ELEVATED BILIRUBIN NOS
(Sx) ELEVATED ALKALINE PHOSPHATASE
(Dx) VASCULITIS — Reporter

Narrative: This US spontaneous postmarketing case reported by a pharmacy intern involves a patient (age and gender not provided) who was receiving ARAVA (leflunomide). Dosage, indication, and therapy dates were not provided. On an unspecified date, the patient experienced an elevated bilirubin NOS, jaundice, elevated alkaline phosphatase NOS, and vasculitis. Outcome is unknown. *

6. Relevant tests/laboratory data, including dates

7. Other relevant history, including preexisting medical conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)

NO MENTION OF RELEVANT DISEASE

C. Suspect medication(s)

1. Name (give labeled strength & mfr/labeler if known)

#1 LEFLUNOMIDE (ARAVA) Tablets

#2

2. Dose, frequency & route used

#1

#2

3. Therapy dates (if unknown, give duration) (m/d/y for best estimate)

#1

#2

4. Diagnosis for use (indication)

#1 UNKNOWN

#2

5. Event abated after use stopped or dose reduced

#1 [ ] yes [ ] no [ ] doesn't apply

#2 [ ] yes [ ] no [ ] doesn't apply

6. Lot # (if known)

#1 UNK

#2

7. Exp. date (if known)

#1

#2

8. Event reappeared after reintroduction

#1 [ ] yes [ ] no [ ] doesn't apply

#2 [ ] yes [ ] no [ ] doesn't apply

9. NDC # - for product problems only (if known)

#1 #2

10. Concomitant medical products and therapy dates (exclude treatment of event)

UNKNOWN DRUG (UNKNOWN DRUG)

G. All manufacturers

1. Contact office - name/address (& mfr'ng site for devices)

Hoechst Marion Roussel, Inc.
10236 Marion Park Drive
Kansas City, MO
64137

DEC 20 [illegible]

2. Phone number: (816) 966-5000

3. Report source (check all that apply)
- [ ] foreign
- [ ] study
- [ ] literature
- [ ] consumer
- [X] health professional
- [ ] user facility
- [ ] company representative
- [ ] distributor
- [ ] other:

4. Date received by manufacturer (m/d/y/yr): 12/09/1999

5. (A)NDA # 20-905
IND #
PLA #
pre-1938 [ ] yes
OTC product [ ] yes

6. If IND, protocol #

7. Type of report (check all that apply)
- [ ] 5-day
- [X] 15-day
- [ ] 10-day
- [ ] periodic
- [X] initial
- [ ] follow-up #

8. Adverse event term(s)

LIVER FAILURE, JAUNDICE, BILIRUBINEMIA, ALKALINE PHOSPHATASE INCREASED, VASCULITIS

9. Mfr. report number

199922130HMRI

E. Initial reporter

1. Name, address & phone #

JENNIFER SMITH
PITT COUNTY MEMORIAL HOSPITAL
PO BOX 6020
GREENVILLE, NC 27835 *

DEC 17 1999

2. Health professional? [ ] yes [ ] no

3. Occupation

4. Initial reporter also sent report to FDA [ ] yes [ ] no [ ] unk

FDA

Domain Facsimile of FDA Form 3500A

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

* Item completed on continuation pages

B.2. Other outcome

medically important

B.5. Describe event or problem

[continuation:] Relevant medical history and relevant concomitant medications were not provided.

Reporter's assessment of causal relationship: Not provided.

Addendum 09-Dec-1999: A physician reported the diagnosis of hepatic failure. No other information was received.

Reporter's assessment of causal relationship: Not provided.

Reporter assessment of the causal relationship between the adverse event and suspect drug:
[_] Possible [_] Unlikely [_] Unrelated
[_] Insufficient Data
If unlikely/unrelated, provide alternative explanation:
[_] Illness [_] Concomitant Drug [_] Other

E.1. Name, address & phone #

[continuation:] UNITED STATES 252-816-4257

DEC 20 [illegible]

DEC 17 1999

MedWatch Forms

(USA)

Patient Number 15

Individual Safety Report

3923098-3-00-01

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Aventis Pharmaceuticals, Inc.

Domain Facs/mle

Approved by FDA on 3/22/94

Mfr report # 200214805US

UF/Dist report #

FDA Use Only

A. Patient information

1. Patient identifier: AG in confidence
2. Age at time of event: 55 yrs or ____ Date of birth: UNK
3. Sex: ☐ female ☒ male
4. Weight: ____ lbs or ____ kgs

B. Adverse event or product problem

1. ☒ Adverse event and/or ☐ Product problem (e.g., defects/malfunctions)

2. Outcomes attributed to adverse event (check all that apply)
- ☐ death ____ (mo/day/yr)
- ☐ life-threatening
- ☒ hospitalization - initial or prolonged
- ☐ disability
- ☐ congenital anomaly
- ☐ required intervention to prevent permanent impairment/damage
- ☐ other: ____

3. Date of event (mo/day/yr): 04/27/2002

4. Date of this report (mo/day/yr): 05/22/2002

5. Describe event or problem

	Event (Nature of Event)	Dx Origin
(Dx)	ACUTE HEPATOCELLULAR INJURY	Reporter
(Sx)	ELEVATED AST (IN 1000'S--PEAK 6000)	
(Sx)	ELEVATED ALT (IN 1000'S--PEAK 6000)	
(Sx)	ELEVATED TOTAL BILIRUBIN (PEAK--9)	
(Sx)	BILIRUBIN INCREASED TO 22	
(Sx)	INR--3.1	
(Sx)	CHEMICAL HEPATITIS	
(Dx)	INTERSTITIAL PNEUMONITIS SECONDARY TO SCLERODERMA	Reporter
(Sx)	PRODUCTIVE COUGH WITH SOME HEMOPTYSIS	
(Sx)	DRY COUGH	
(Sx)	PULMONARY FIBROSIS	
(Sx)	INTERSTITIAL INFILTRATES	*

6. Relevant tests/laboratory data, including dates

7. Other relevant history, including preexisting medical conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)

QUESTIONABLE COLLAGEN DISORDER, NO KNOWN DRUG ALLERGIES, ALCOHOL USE, alcohol use HYPERTENSION

MAY 2 4 2002

C. Suspect medication(s)

1. Name (give labeled strength & mfr/labeler, if known)
- #1 LEFLUNOMIDE (ARAVA) Tablets
- #2 LEFLUNOMIDE (ARAVA) Tablets

2. Dose, frequency & route used
- #1 20 MG QD PO
- #2 *

3. Therapy dates (if unknown, give duration) from/to (or best estimate)
- #1 *
- #2 Duration: 3 days

4. Diagnosis for use (indication)
- #1 SCLERODERMA
- #2 SCLERODERMA

5. Event abated after use stopped or dose reduced
- #1 ☐ yes ☐ no ☒ doesn't apply
- #2 ☐ yes ☐ no ☒ doesn't apply

6. Lot # (if known)
- #1 UNK
- #2 UNK

7. Exp. date (if known)
- #1
- #2

8. Event reappeared after reintroduction
- #1 ☐ yes ☐ no ☒ doesn't apply
- #2 ☐ yes ☐ no ☒ doesn't apply

9. NDC # - for product problems only (if known)
- #1
- #2

10. Concomitant medical products and therapy dates (exclude treatment of event)

VERAPAMIL Unknown to 04/27/2002

G. All manufacturers

1. Contact office - name/address (& mfring site for devices)

Aventis Pharmaceuticals, Inc.
300 Somerset Corporate Blvd.
Bridgewater, NJ
08807-2854

2. Phone number: (908)243-6000

3. Report source (check all that apply)
- ☐ foreign
- ☐ study
- ☐ literature
- ☐ consumer
- ☒ health professional
- ☐ user facility
- ☐ company representative
- ☐ distributor
- ☐ other:

4. Date received by manufacturer (mo/day/yr): 05/09/2002

5. (A)NDA # 20-905
- IND # ____
- PLA # ____
- pre-1938 ☐ yes
- OTC product ☐ yes

6. If IND, protocol #

7. Type of report (check all that apply)
- ☐ 5-day ☒ 15-day
- ☐ 10-day ☐ periodic
- ☒ initial ☐ follow-up # ____

8. Adverse event term(s)

HEPATOCELLULAR DAMAGE, ASPARTATE AMINOTRANSFERASE INCREASED, ALANINE AMINOTRANSFERASE INCREASED, BLOOD BILIRUBIN INCREASED, BLOOD BILIRUBIN *

9. Mfr. report number: 200214805US

E. Initial reporter

1. Name, address & phone #

GUILLERMO GUZMAN MD
7502 GREENVILLE AVE
SUITE 450
DALLAS, TX 75231 *

DSS

MAY 2 8 2002

2. Health professional? ☒ yes ☐ no

3. Occupation: Rheumatology

4. Initial reporter also sent report to FDA: ☐ yes ☐ no ☐ unk

FDA

Domain Facsimile of FDA Form 3500A

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

Item completed on continuation pages.

B.5. Describe event or problem

[continuation:]
(Dx) RIGHT-SIDED HEART FAILURE Reporter
(Sx) DILATED CARDIOMYOPATHY
(Sx) ALTERED MENTAL STATUS
(Sx) DECREASED EJECTION FRACTION (10%)
(Sx) CORONARY PLAQUES
(Dx) HEPATIC CONGESTION SECONDARY TO R-SIDED HEART FAILURE Reporter
(Sx) TOTAL BILIRUBIN (26MG/DL)
(Sx) INCREASED TRANSAMINASES IN 300'S
(Sx) INCREASED PT/INR

Narrative: Initial report 09-May-2002: This postmarketing case was reported by 2 different rheumatologists (prescribing physician and treating physician) via a sales representative. It involves a 55-year-old male patient receiving leflunomide 20mg daily since Feb 01 for scleroderma. He was given a loading dose of 100mg a day x 3 days. He consumed 1-2 alcoholic drinks/day while receiving Arava, as per the patient's wife. Concomitant medications include Verapamil, which was changed to Atenolol upon admission to the hospital on 27-Apr-2002. In Feb 2002, the patient started to experience dry cough which he was not treated for. In April 2002, 3 weeks prior to his admission to the hospital, he started to experience productive cough with hemoptysis. He was not treated for this event as well. On 27-Apr-02, he was advised to go to the ER by the prescribing physician because the patient complained of a mild respiratory infection. In the ER, CXR revealed possible pneumonia, and he was admitted to the hospital. At this time, his LFT's were elevated (ALT and AST were both in 200's). Arava was discontinued. He was started on Levaquin (levofloxacin) 500mg PO once a day x 7 days. His respiratory condition progressively worsened. He had a complete work-up with ID, pulmonology, and GI consults (nos). His TB test was negative (patient travels). The results of the cultures are pending. Four days after the admission, patient was reported to be in liver failure with AST and ALT in the thousands with the peak of 6000, total bilirubin of 9 (peak), and INR of 3.1. On 01-May-2002, Arava washout procedure was started with cholestyramine 3 grams TID. He was seen by a Gastroenterologist who diagnosed him with chemical hepatitis secondary to Arava. Patient started to improve, and he was discharged home on 08-May-2002. He was discharged on Prednisone 60 mg once a day for the diagnosis of interstitial pneumonitis secondary to scleroderma. The treating physician reported that the patient recovered and not in liver failure as of 08-May-2002. As per the prescribing physician, patient's baseline LFT's were normal. He had regular LFT's (-every 2 months) performed, which were all normal. His last LFT's was 1-2 months prior to the hospital admission (normal).

Additional information from 13-May-2002 from the sales representative indicated the patient had leflunomide "washed out of his system" (NOS). The patient just left the hospital a couple of days ago.
Additional information from 14-May-2002: The patient's physician indicated the patient was discharged from the hospital on Thuraday, 09-May-2002 with a bilirubin of 6.7. He was readmitted yesterday on 13-May-2002 with altered mental status and an elevated bilirubin of 22. The physician's causal assessment of the relationship between the suspected liver failure and Arava is related.
Additional information was received on 16-May-2002: According to the reporting rheumatologist, the patient has pure scleroderma, not rheumatoid arthritis. In the first hospital admission, the LFT's increased with maximum value of the ALT and AST in the 6000's (units not provided). The total bilirubin reached a maximum value of 9 mg/dl. A cholestyramine washout was done at 3 grams TID for a total of 13 days. During the hospitalization, the patient was diagnosed with interstitial lung disease, which was assessed to be compatible with Scleroderma Lung. The chest CT scan showed pulmonary fibrosis with interstitial infiltrates. At the time of his discharge from the first hospitalization, the patient's total bilirubin was 6.7 mg/dl and the transaminases were in the 300's. The patient's discharge medications included Prevacid, Atenolol and Prednisone.
At the time of the second hospital admission, the patient presented with altered mental status, and lab tests showed transaminases in the 300's and a total bilirubin of 26 mg/dl. The patient was found to be in right-sided heart failure. An echocardiogram was done, and it showed dilated cardiomyopathy with ejection fraction of 10%. A GI consultant evaluated the patient and assessed the increased bilirubin level to be secondary to right-sided heart *

DSS

B.5. Describe event or problem

(continuation) failure. The GI consultant ruled out the diagnosis of liver failure; according to the GI specialist, the patient was not in liver failure. The GI consultant assessed that the abnormal liver function tests were associated with hepatic congestion secondary to right-sided heart failure, possible alcoholic liver disease and possible drug-induced hepatitis. It was revealed that the patient had a significant history of alcohol use. The etiology for the right-sided CHF has not been clearly established to date. It may be associated with the patient's pulmonary condition, the scleroderma lung. Also, the cardiomyopathy may be associated with the alcohol use. Furthermore, the high-resolution chest CT scan revealed plaques in the coronary arteries, suggestive of coronary artery disease. According to the GI consult, the possible drug-induced hepatitis appears to be associated with Arava therapy, not Levaquin. Liver biopsy was not done due to elevated PT and INR.
According to the rheumatologist, the patient has pure scleroderma; there is no clinical evidence of rheumatoid arthritis. He does not believe the hepatitis to be autoimmune in nature. In terms of his current status, the patient is improving. The patient has recently been transferred out of the ICU. The patient's mental status and the LFT's, including PT/INR, are also improving.

Event	Serious	Dechal	Rechal	Rpt.Causality	Alternative Explanation
(Dx) ACUTE HEPATOCELLULAR INJURY	YES	NA	NA	Probable	other known or suspected cause
(Sx) ELEVATED AST (IN 1000'S--PEAK 6000)					
(Sx) ELEVATED ALT (IN 1000'S--PEAK 6000)					
(Sx) ELEVATED TOTAL BILIRUBIN (PEAK--9)					
(Sx) BILIRUBIN INCREASED TO 22					
(Sx) INR--3.1					
(Sx) CHEMICAL HEPATITIS					
(Dx) INTERSTITIAL PNEUMONITIS SECONDARY TO SCLERODERMA	YES	NA	NA		underlying/concomitant illness
(Sx) PRODUCTIVE COUGH WITH SOME HEMOPTYSIS					
(Sx) DRY COUGH					
(Sx) PULMONARY FIBROSIS					
(Sx) INTERSTITIAL INFILTRATES					
(Dx) RIGHT-SIDED HEART FAILURE	YES	NA	NA		underlying/concomitant illness
(Sx) DILATED CARDIOMYOPATHY					
(Sx) ALTERED MENTAL STATUS					
(Sx) DECREASED EJECTION FRACTION (10%)					
(Sx) CORONARY PLAQUES					
(Dx) HEPATIC CONGESTION SECONDARY TO R-SIDED HEART FAILURE	YES	NA	NA		underlying/concomitant illness
(Sx) TOTAL BILIRUBIN (26MG/DL)					
(Sx) INCREASED TRANSAMINASES IN 300'S					
Sx) INCREASED PT/INR					

C.3. Therapy dates (if unknown, give duration) (mo/day/yr) (Suspect #1)

02/??/2001 to 04/27/2002 Duration: 1 year 2 months

C.2. Dose, frequency & route used (Suspect #2)

100 (LOADING DOSE) MG QD PO

G.8. Adverse event term(s)

[continuation:] INCREASED, INTERNATIONAL NORMALISED RATIO INCREASED, HEPATITIS NOS, PNEUMONITIS NOS, HAEMOPTYSIS, COUGH, PULMONARY FIBROSIS, LUNG INFILTRATION NOS, CARDIAC FAILURE CONGESTIVE, CONGESTIVE (DILATED) CARDIOMYOPATHY, MENTAL STATUS CHANGES, EJECTION FRACTION DECREASED, CORONARY ARTERY DISEASE NOS, HEPATIC CONGESTION, BLOOD BILIRUBIN INCREASED, TRANSAMINASE NOS INCREASED, PROTHROMBIN TIME PROLONGED

E.1. Name, address & phone #

[continuation:] UNITED STATES 214-691-3393

MedWatch Forms

(USA)

Patient Number 16

3959092-6-00-01

entis Pharmaceuticals, Inc.

Domain Facsimile

Approved by FDA on 3/22/94

Mfr report # 200215633US

UF/Diet report #

FDA Use Only

MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

A. Patient information

1. Patient identifier	2. Age at time of event:	3. Sex	4. Weight
CL	49 yrs or	☐ female	____ lbs or
in confidence	Date of birth: 10/12/1952	☒ male	____ kgs

B. Adverse event or product problem

1. ☒ Adverse event and/or ☐ Product problem (e.g., defects/malfunctions)

2. Outcomes attributed to adverse event (check all that apply)

- ☐ death ____ (mo/day/yr)
- ☒ life-threatening
- ☒ hospitalization - initial or prolonged
- ☐ disability
- ☐ congenital anomaly
- ☐ required intervention to prevent permanent impairment/damage
- ☐ other: ____

3. Date of event (mo/day/yr)

4. Date of this report (mo/day/yr): 08/01/2002

5. Describe event or problem

Event (Nature of Event)	Dx Origin
(Dx) ACUTE HEPATITIS	Reporter
(Dx) FULMINANT LIVER FAILURE	Reporter
(Sx) NAUSEA	
(Sx) VOMITING	
(Sx) INCREASED ALT (1500. 6000, 2400)	
(Sx) INCREASED AST (1000, 6000, 2000)	
(Sx) INCREASED INR (4.3, 2.4, 6.5)	
(Sx) WEAKNESS	
(Sx) FATIGUE	
(Sx) CONFUSION	
(Sx) ENCEPHALOPATHY	
(Sx) BODY PAIN	
(Sx) CHEST PAIN	
(Sx) CHILLS	

*

6. Relevant tests/laboratory data, including dates

7. Other relevant history, including preexisting medical conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)

PPD POSITIVE, NO KNOWN DRUG ALLERGIES, nicotine use
RHEUMATOID ARTHRITIS, HYPERTENSION, HERNIATED DISK, QUESTIONABLE HEPATITIS B, BORDERLINE ELEVATED LIVER FUNCTION TESTS, DEPRESSION, ANXIETY *

C. Suspect medication(s)

1. Name (give labeled strength & mfr/labeler, if known)

#1 LEFLUNOMIDE (ARAVA) Tablets

#2 INFLIXIMAB (REMICADE)

2. Dose, frequency & route used	3. Therapy dates (if unknown, give duration) from/to (or best estimate)
#1 20 MG QD PO	#1 *
#2 QW PO	#2 Unknown to 05/20/2002

4. Diagnosis for use (indication)

#1 RHEUMATOID ARTHRITIS

#2 RHEUMATOID ARTHRITIS

5. Event abated after use stopped or dose reduced

#1 ☐ yes ☐ no ☑ doesn't apply

#2 ☐ yes ☐ no ☐ doesn't apply

6. Lot # (if known)	7. Exp. date (if known)
#1 UNK	#1
#2	#2

8. Event reappeared after reintroduction

#1 ☐ yes ☐ no ☒ doesn't apply

#2 ☐ yes ☐ no ☐ doesn't apply

9. NDC # - for product problems only (if known)

#1 #2

10. Concomitant medical products and therapy dates (exclude treatment of event)

FOLATE SODIUM
PREDNISONE Unknown to 05/20/2002
CALCIUM

G. All manufacturers

1. Contact office - name/address (& mfring site for devices)

Aventis Pharmaceuticals, Inc.
300 Somerset Corporate Blvd.
Bridgewater, NJ
08807-2854

2. Phone number: (908)243-6000

3. Report source (check all that apply)

- ☐ foreign
- ☐ study
- ☐ literature
- ☐ consumer
- ☒ health professional
- ☐ user facility
- ☐ company representative
- ☐ distributor
- ☐ other:

4. Date received by manufacturer (mo/day/yr): 07/24/2002

5. (A)NDA # 20-905
IND # ____
PLA # ____
pre-1938 ☐ yes
OTC product ☐ yes

6. If IND, protocol #

7. Type of report (check all that apply)

- ☐ 5-day ☒ 15-day
- ☐ 10-day ☐ periodic
- ☐ Initial ☒ follow-up # 1

8. Adverse event term(s)

HEPATITIS ACUTE, HEPATIC FAILURE, NAUSEA, VOMITING NOS, ALANINE AMINOTRANSFERASE INCREASED, ASPARTATE AMINOTRANSFERASE INCREASED, INTERNATIONAL *

9. Mfr. report number: 200215633US

E. Initial reporter

1. Name, address & phone #

ABLE TIELLO MD
420 DELAWARE SE
MINNEAPOLIS, MN 55455
UNITED STATES 612-386-1616

DSS
AUG 06 2002

2. Health professional?	3. Occupation	4. Initial reporter also sent report to FDA
☒ yes ☐ no		AUG 05 2002 ☐ yes ☐ no ☐ unk

FDA

Domain Facsimile of FDA Form 3500A

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

Item completed on continuation pages.

A. Patient information

1. Patient identifier: CL in confidence
2. Age at time of event: or Date of birth:
3. Sex: ☐ female ☐ male
4. Weight: ____ lbs or ____ kgs

B. Adverse event or product problem

1. ☐ Adverse event and/or ☐ Product problem (e.g., defects/malfunctions)
2. Outcomes attributed to adverse event (check all that apply)
   - ☐ death ___ (mo/day/yr)
   - ☐ life-threatening
   - ☐ hospitalization - initial or prolonged
   - ☐ disability
   - ☐ congenital anomaly
   - ☐ required intervention to prevent permanent impairment/damage
   - ☐ other:
3. Date of event (mo/day/yr)
4. Date of this report (mo/day/yr)
5. Describe event or problem

6. Relevant tests/laboratory data, including dates

7. Other relevant history, including preexisting medical conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)

C. Suspect medication(s)

1. Name (give labeled strength & mfr/labeler, if known)
   - #3 METHOTREXATE
   - #4 METHOTREXATE
2. Dose, frequency & route used
   - #3 7.5 MG QW
   - #4 5 MG QW
3. Therapy dates (if unknown, give duration) from/to (or best estimate)
   - #3 Unknown to 04/08/2002
   - #4 *
4. Diagnosis for use (indication)
   - #3 RHEUMATOID ARTHRITIS
   - #4 RHEUMATOID ARTHRITIS
5. Event abated after use stopped or dose reduced
   - #3 ☐ yes ☐ no ☐ doesn't apply
   - #4 ☐ yes ☐ no ☐ doesn't apply
6. Lot # (if known)
   - #3
   - #4
7. Exp. date (if known)
   - #3
   - #4
8. Event reappeared after reintroduction
   - #3 ☐ yes ☐ no ☐ doesn't apply
   - #4 ☐ yes ☐ no ☐ doesn't apply
9. NDC # - for product problems only (if known)
   - #3
   - #4
10. Concomitant medical products and therapy dates (exclude treatment of event)

G. All manufacturers

1. Contact office - name/address (& mfring site for devices)
2. Phone number
3. Report source (check all that apply)
   - ☐ foreign
   - ☐ study
   - ☐ literature
   - ☐ consumer
   - ☐ health professional
   - ☐ user facility
   - ☐ company representative
   - ☐ distributor
   - ☐ other:
4. Date received by manufacturer (mo/day/yr)
5. (A)NDA # ____ IND # ____ PLA # ____ pre-1938 ☐ yes OTC product ☐ yes
6. If IND, protocol #
7. Type of report (check all that apply)
   - ☐ 5-day ☐ 15-day
   - ☐ 10-day ☐ periodic
   - ☐ Initial ☐ follow-up #____
8. Adverse event term(s)
9. Mfr. report number

E. Initial reporter

1. Name, address & phone #

DSS
AUG 06 2002

2. Health professional? ☐ yes ☐ no
3. Occupation
4. Initial reporter also sent report to FDA ☐ yes ☐ no ☐ unk

AUG 05 2002

FDA

Domain Facsimile of FDA Form 3500A

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

Item completed on continuation pages.

3959092-6-00-03

entis Pharmaceuticals, Inc.

Approved by FDA on 3/22/94

Domain Facsimile

Mfr report # 2002156330B

UF/Dist report #

FDA Use Only

MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

A. Patient information

1. Patient identifier	2. Age at time of event:	3. Sex	4. Weight
CL in confidence	or ____ Date of birth:	☐ female ☐ male	____ lbs or ____ kgs

B. Adverse event or product problem

1. ☐ Adverse event and/or ☐ Product problem (e.g., defects/malfunctions)

2. Outcomes attributed to adverse event (check all that apply)

- ☐ death ____ (mo/day/yr)
- ☐ life-threatening
- ☐ hospitalization - initial or prolonged
- ☐ disability
- ☐ congenital anomaly
- ☐ required intervention to prevent permanent impairment/damage
- ☐ other: ____

3. Date of event (mo/day/yr)	4. Date of this report (mo/day/yr)

5. Describe event or problem

6. Relevant tests/laboratory data, including dates

7. Other relevant history, including preexisting medical conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)

C. Suspect medication(s)

1. Name (give labeled strength & mfr/labeler, if known)

#5 ISONIAZID

#6

2. Dose, frequency & route used

#5

#6

3. Therapy dates (if unknown, give duration) from/to (or best estimate)

#5

#6

4. Diagnosis for use (indication)

#5 PPD POSITIVE

#6

5. Event abated after use stopped or dose reduced

#5 ☐ yes ☐ no ☐ doesn't apply

#6 ☐ yes ☐ no ☐ doesn't apply

6. Lot # (if known)

#5

#6

7. Exp. date (if known)

#5

#6

8. Event reappeared after reintroduction

#5 ☐ yes ☐ no ☐ doesn't apply

#6 ☐ yes ☐ no ☐ doesn't apply

9. NDC # - for product problems only (if known)

#5

#6

10. Concomitant medical products and therapy dates (exclude treatment of event)

G. All manufacturers

1. Contact office - name/address (& mfring site for devices)

2. Phone number

3. Report source (check all that apply)

- ☐ foreign
- ☐ study
- ☐ literature
- ☐ consumer
- ☐ health professional
- ☐ user facility
- ☐ company representative
- ☐ distributor
- ☐ other:

4. Date received by manufacturer (mo/day/yr)

5. (A)NDA # ____
IND # ____
PLA # ____
pre-1938 ☐ yes
OTC product ☐ yes

6. If IND, protocol #

7. Type of report (check all that apply)

- ☐ 5-day ☐ 15-day
- ☐ 10-day ☐ periodic
- ☐ initial ☐ follow-up # ____

8. Adverse event term(s)

9. Mfr. report number

E. Initial reporter

1. Name, address & phone #

DSS

AUG 06 2002

2. Health professional?	3. Occupation	4. Initial reporter also sent report to FDA
☐ yes ☐ no		☐ yes ☐ no ☐ unk

AUG 05 2002

FDA

Domain Facsimile of FDA Form 3500A

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

Item completed on continuation pages.

B.5. Describe event or problem

[continuation:]
(Sx) COUGH
(Sx) DARK COLORED URINE
(Sx) OBTUNDED
(Sx) ABDOMINAL PAIN
(Sx) LOSS OF APPETITE
(Sx) SICKNESS
(Sx) JAUNDICE
(Dx) HYPOPHOSPHATEMIA — Reporter
(Dx) NEW LUNG LESION ON CHEST X-RAY — Reporter
(Sx) SMALL BILATERAL PLEURAL EFFUSIONS

Narrative: Initial report: This spontaneous postmarketing case, received from a physician, involves a 49 year old Vietnamese male who initiated therapy with Arava (leflunomide) 20mg daily in early Apr-2002 for rheumatoid arthritis. It is not indicated if the patient received the loading dose of leflunomide. Leflunomide, methotrexate, Remicade (infliximab) and prednisone were discontinued on 20-May-2002 following his presentation to a clinic with jaundice. He did not undergo the cholestyramine washout. The patient had approximately 6 weeks of leflunomide therapy before it was discontinued. A chest x-ray done on 21-May-2002 revealed right upper lobe pleural thickening with possible parenchymal involvement, possibly a re-activation of tuberculosis. A previous chest x-ray done in Sep-2001 was normal. On 22-May-2002 the patient presented to a local hospital with a one-week history of nausea and vomiting, generalized body pain, chest pain, fever, chills, cough, weak, tired, dark colored urine, abdominal pain, marked loss of appetite and sickness. He denied diarrhea and skin itching. On 22-May-2002 his ALT was 1841, AST was 1502, bilirunin was 1.4, BUN was 27, creatinine was 1.4, sodium was 134, potassium was 4.2, chloride was 99, CO2 was 27, anion gap was 8, hemoglobin was 16.6, and white count was 5.5. Urinalysis was positive for bilirubin, otherwise normal. Over the next 4 days the transaminases peaked around 6000 with an INR of 4.3. On 28-May-2002 the patient was transferred to another hospital. At that time his INR was 2.4, ALT was 2000 and AST was 2400. On 30-May-2002 the patient's INR peaked at 6.5. The patient underwent liver transplantation on 01-Jun-2002 and is currently recovering in the intensive care unit in stable condition. A renal ultrasound was done which was normal. No liver biopsy was done prior to the transplant. An abdominal ultrasound was done on 29-May-2002 which revealed the following: gallbladder appears ill defined with thickened walls with the suggestion of fluid within the walls, these changes may represent changes from hepatitis although cholecystitis cannot be excluded, liver is normal in echogenicity, (which can occur in the setting of hepatitis), unremarkable Doppler examination of the liver, small bilateral pleural effusions, and small amount of free fluid in the abdomen. The anatomic pathology of the liver and gallbladder revealed submassive necrosis of the liver and mild mucosal ischemic changes of the gallbladder. Section of the liver showed a proliferation of the bile ductules with small foci of hepatocytes with regenerative changes. These changes are consistent with a toxic insult. The following labs were provided:

	5/28	5/29	5/30	5/31	6/1	6/2	6/3	6/4	6/5
ALT	2495	2685	1896	1294,518	596	560	468	448	287
Alk phos	189	256	186	163	137	112	95	110	88
direct bili				0.2	0.5		0.3	0.3	0.2
total bili	11.0	14.4	13.2	13.8,7.4	3.0	1.2	0.9	1.0	0.9
CMV IgG Ab			123						
EB, IgG		4.56							
Hgb	11.4		12.0	10.5,9.1, 10.2,9.5, 11.1,12.6, 14.3	14.6,14.4, 14.6,14.6	13.3	13.2	14.6	13.5

DSS

AUG 0 6 2002

HBsAg was positive, total HAAb was positive, HAAb, IgM was negative, HBcAb total was positive and hepatitis B quant was 0.208.

Concomitant medications included methotrexate, infliximab, calcium, folate, and isoniazid for tuberculosis prophylaxis. Medical history is significant for rheumatoid arthritis, hypertension, borderline elevated liver *

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B.5. Describe event or problem

[continuation:] function tests, depression, anxiety disorder and no known drug allergies.

Reporter's assessment of causal relationship: The patient was on 3 other medications that are known to be hepatotoxic, but the role of leflunomide cannot be ruled out.

Addendum for follow up received 24-Jul-2002: The following information was provided by the nurse: Patient is doing fair post transplant. His labs are much improved but is still experiencing a lot of pain and fatigue. The following labs from 05-Jul-2002 were provided: Alk phos=60 (40-150), ALT=<3 (0-70), AST=12 (0-55), conjugated bilirubin=0 (0-0.3), delta bilirubin=0 (0-0.4), total bilirubin=0.3 (0.2-1.3), urea nitrogen=17 (5-24), calcium=8.8 (8.2-10.4), chloride=102 (94-109), CO2 total=28 (20-32), creatinine=1.3 (0.8-1.5), glucose=250 (60-115), potassium=4.6 (3.4-5.3), sodium=138 (133-144), total protein=6.9 (6-8.2).

Event	Serious	Dechal	Rechal	Rpt.Causality	Alternative Explanation
(Dx) ACUTE HEPATITIS	YES	UNK	UNK	Possible	possibly associated with concomitant drug(s)
(Dx) FULMINANT LIVER FAILURE	YES	UNK	UNK	Possible	possibly associated with concomitant drug(s)
(Sx) NAUSEA					
(Sx) VOMITING					
(Sx) INCREASED ALT (1500. 6000, 2400)					
(Sx) INCREASED AST (1000, 6000, 2000)					
(Sx) INCREASED INR (4.3, 2.4, 6.5)					
(Sx) WEAKNESS					
(Sx) FATIGUE					
(Sx) CONFUSION					
(Sx) ENCEPHALOPATHY					
(Sx) BODY PAIN					
(Sx) CHEST PAIN					
(Sx) CHILLS					
(Sx) COUGH					
(Sx) DARK COLORED URINE					
(Sx) OBTUNDED					
(Sx) ABDOMINAL PAIN					
(Sx) LOSS OF APPETITE					
(Sx) SICKNESS					
(Sx) JAUNDICE					
(Dx) HYPOPHOSPHATEMIA	NO	NA	NA		underlying/concomitant illness
(Dx) NEW LUNG LESION ON CHEST X-RAY	YES	NA	NA		underlying/concomitant illness
(Sx) SMALL BILATERAL PLEURAL EFFUSIONS					

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*. Other relevant history, including preexisting medical conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)

[continuation:] Race: ASIAN

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C.3. Therapy dates (if unknown, give duration) (mo/day/yr) (Suspect #1)

04/??/2002 to 05/20/2002 Duration: 6 weeks

C.3. Therapy dates (if unknown, give duration) (mo/day/yr) (Suspect #4)

04/08/2002 to 05/20/2002 Duration: 6 weeks 1 day

G.8. Adverse event term(s)

[continuation:] NORMALISED RATIO INCREASED, WEAKNESS, FATIGUE, CONFUSION, ENCEPHALOPATHY NOS, PAIN NOS, CHEST PAIN, RIGORS, COUGH, CHROMATURIA, DEPRESSED LEVEL OF CONSCIOUSNESS, ABDOMINAL PAIN NOS, ANOREXIA, ILL-DEFINED DISORDER NOS, JAUNDICE NOS, HYPOPHOSPHATAEMIA, LUNG DISORDER NOS, PLEURAL EFFUSION